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AN EXPLORATORY STOCHASTIC MODEL FOR TOXIC EFFECTS ON CELLS

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AN EXPLORATORY STOCHASTIC MODEL FOR TOXIC EFFECTS ON CELLS

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Abstract

A multivariate dynamic Markov model is formulated to describe the possible effect of a generic chemical toxin on a generic cell population in an organ. Asymptotic methods (large cell population) are used to show that numbers and toxin may be jointly Gaussian/normally distributed; the joint stochastic process is approximately Ornstein-Uhlenbeck. Application to dose-response, and hence risk analysis, is briefly discussed.

EXECUTIVE SUMMARY

This paper presents a generic model for the influence upon the cells in an organ caused by dosage by a chemical toxin. The model is presently non-specific to either organ or toxin, but provides a starting point for specialization. The model is probabilistic/stochastic without requiring computer simulation (it relies on asymptotics appropriate for organs containing a large number of interactive cells).

The organ disfunctionality associated with toxin input that is modeled is the (probability distribution of the) number of functionally active cells present: that number tends to be reduced by toxin input. Inter-cell signalling is modeled by a pairing device; this functionality is due for later elaboration. The effects of cell death by necrosis and apoptosis are modeled. The present model omits explicit consideration of such issues as spatiality of cells within organs, enzyme function and other important features.

Application of the present model is made to consideration of the shape of a dose-response function at low doses.

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1. Introduction

Application of laboratory toxicology data to environmental and human problems of risk assessment almost always requires extrapolation of the data from the experimentally used dose regimen to the exposure conditions of practical concern, and from the animal species tested to the species of concern (usually man). This extrapolation and estimation process is known as *chemical risk assessment*. The risk assessment process has undergone considerable evolution in the last ten years, moving from a qualitative basis for decision making to an increasingly quantitative basis, and from the use of default assumptions to the application of mathematical models as tools upon which to base decisions. In the context of determining safe human exposure limits to potentially toxic chemicals, there are two sub-tasks to be accomplished: estimation of low dose risk in animals and the subsequent conversion of animal risk estimates to human risk estimates.

Dose extrapolation, the first sub-task, can be accomplished either by assuming biological response varies linearly with dose, or by using physiologically-based pharmacokinetic (PBPK) models. Multi-compartment physiological models are formulated using actual tissue volumes from the experimental and target species and actual perfusion rates to provide for

chemical transport between the compartments. Thus the pharmacokinetics of high to low-dose extrapolation become amenable to calculation, and external measures of dose can be translated to concentrations in the target organ (internal dose). Target-organ chemical concentration may be translated into estimates of risk if a mechanistically-based model can be used to relate chemical presence in the organ to harmful outcome. Such models exist for carcinogens, in the form of the widely-used linearized multistage model. This model is based on the generalized concept that chemical alteration of the cellular genes may give rise to permanent, heritable changes in the genetic information stored in the cell nucleus and lead to phenotypic changes in the altered cells that ultimately cause the formation of malignant tumors.

Unfortunately, no similar models exist for chemical toxic effects other than carcinogenesis. The mathematical expression of even the relatively simple concept of genetic alteration leading to cancer involves significant simplification of biological reality and significant mathematical complexity. This state of affairs is exacerbated when one attempts to accurately describe the interactions leading to loss of cell function and cell death in tissues of a whole animal. The multi-layered control and response systems present in an intact living animal are poorly understood and have not been modeled as yet. Nonetheless, these control mechanisms defend against the majority of toxic effects observed as a result of chemical exposure, and their failure represents most of what is observed as the expression of toxicity.

This paper describes initial formulations of models describing cellular response to toxic insult. Our model formulation takes into account aspects of the current state of knowledge concerning the control and regulation of cellular

properties in tissue. The design of this model is not to provide a detailed description of the response of specific organs to toxic insult, but rather to begin the process of mathematically describing the recent significant advances in knowledge that have been made in cell biology, hormonal regulation, and hormetic control mechanisms. Considerable extension of model formulation will be needed to apply it to specific organs, since the complex geometry of organ architecture is not present. To have included complex, three-dimensional relationships between different cell types would have increased the mathematical complexity considerably. The current formulation of the model is suitable for experimental evaluation in cell culture if the experimental conditions are properly chosen.

2. Biological Background

The tissue making up organs almost always involves a complex geometrical juxtaposition of several cell types having specific and often overlapping functions. This tissue architecture is maintained by the presence of a nonliving matrix of proteins collectively known as a basement membrane. Interactions between this membrane and the cell are known to be critical to its stability as a mature, functioning entity. The whole of the tissue is permeated by branching blood vessels, each generation of which is successively smaller; these serve to provide a constant, stable milieu in which the cells exist. Nutrients, control signals in the form of specific biomolecules, and xenobiotic chemicals are brought to the immediate surroundings of the cell by the vasculature in the tissue and cellular metabolic products; the products of energy metabolism and cellularly derived control biomolecules are removed from the cellular microenvironment by the same means.

The state of the cell at any time is a reflection of its age, the summation of the control chemicals reaching and leaving the cell, the effects of xenobiotic chemicals present, if any, and the state of the cells surrounding it. Cellular contact with the surrounding cells and basement membrane act to supply chemical signals that modulate its activity. A given cell may be (i) nearly quiescent, (ii) active biochemically, i.e., producing metabolites of absorbed materials for its own use or for export, (iii) in a state of stress due to shortage or excess of biochemical molecules, (iv) in a process of programmed cell death (apoptosis), (v) in the process of dying from chemical insult (necrosis), or (vi) dividing to form progenitor cells in response to a need to replace cells already lost; these conditions need not be mutually exclusive at any point in time. Some specific cells may alter or completely change their observable characteristics in response to chemical signals. The most well known of these cells are the pluripotent stem cells of the hemopoetic system.

3. Prototypic Mathematical Models for Cellular Response to a Chemical Toxin

In this section we propose several simple models to describe the interaction between cells and a chemical toxin with which they are in contact. The aim is to describe anti-toxin functionality in a parsimonious manner, so certain details are omitted that can feature in later models.

Consider a collection of interacting cells in proximity in an organ such as the liver. In particular, these may be the cells that line the sinusoids in the liver, the function of which is to remove waste from the blood flowing through.

Focus first on the cell cycle. For present purposes a given cell may be in one of two states: functionally active, i.e. or undergoing mitosis, i.e., *mitotic*; other detailed aspects of the cycle are temporarily ignored. During the functionally

active state occupancy time a cell performs its intended function, i.e., that of removal of nutrients and wastes from contiguous blood flow. Such a cell has a certain natural life time, the duration of which is influenced both by the programmed cell death phenomenon *apoptosis*, but also by the occurrence of an insult, possibly directly from an environmental agent such as a toxic chemical, but also from a metabolite; the latter cause of death is *necrosis*. When a cell dies a chemical message is sent to a neighboring cell *via* the intercellular media commanding that neighbor to divide, or perform mitosis, i.e., go into S and G_2. During the period of a cell's mitosis the original collection of active cells is effectively deprived of two members: the dead one, and the neighbor undergoing mitosis. Note that a dying cell need not always signal the *same* neighbor to become mitotic, but restriction to that situation is not exceptionally special and does lead to quite a simple initial model.

Model D.1. A Deterministic Model Involving Monogamous Cell Pairs.

Consider a monogamous cell pair that alternatively is in mitosis and is functionally active. Suppose $\{X_i, i = 1, 2, \dots\}$ are independently and identically distributed positive random variables that represent the time spent in mitosis for the pair, and $\{L_{1i}, L_{2i}, i = 1, 2, \dots\}$ be the lifetimes of the two paired cells when they are in the functionally active state. We assume the pair's lifetimes are probabilistic, being mutually independently and identically distributed, and are re-sampled after each mitosis event period terminates. The pair dies, in effect, after lifetime $L_i = \min(L_{1i}, L_{2i})$, after which mitosis begins, eventually terminates, and a new pair lifetime begins; so the process continues. If $I_D(t)$ is the indicator function that specifies the state of the pair at t, so

$$I_D(t) = \begin{cases} 1 & \text{if both cells of pair are in totally differentiated state at time } t; \\ 0 & \text{otherwise} \end{cases} \tag{3.1}$$

then

$$P_D(t) = P\{I_D(t) = 1 \mid \text{Both pair members have just entered the totally differentiated state at } t = 0\} \tag{3.2}$$

satisfies a renewal integral equation, see Feller (1966):

$$P_D(t) = 1 - F_L(t) + \int_0^t P_D(t-x)G(dx), \tag{3.3}$$

where

$$F_L(t) = P\{L_{1i} \le t, L_{2i} \le t\} = P\{L \equiv \max(L_{1i}, L_{2i}) \le t\} \tag{3.4}$$

and

$$G(x) = F_L(x) * F_X(x) \equiv \int_0^x F_L(x-y)F_X(dx). \tag{3.5}$$

The argument for (3.3): starting with both pair members freshly back from mitosis the pair is either, (i), still in the functionally active state at time t, an event of probability 1-$F_L(t)$ --the first right-side term of (3.3) -- or, (ii), the pair has cycled, first through its functionally active state and then through mitosis, with the pair starting a new life at time x; this is represented by the integral term of (3.3).

Asymptotics

Renewal theory results, cf. Feller (1966) or Asmussen (1987), tell us that, as time gets long, a limit is approached, expressed as

$$\lim_{t\to\infty} P_D(t) = p_D = \frac{E[L]}{E[L]+E[X]}, \tag{3.6}$$

where $E[L]$ is the mean time of pair residence in the totally differentiated state, and $E[X]$ is the mean time of cell pair's absence for mitosis. Thus the productive fraction of the time, p_D, depends only upon the means of the state residence times and not upon details of their distributions. Of course different cell types, and those with different locations in an organ, might well have different means, and hence different p_D-values. Moreover, both means could be expected to

respond to a toxic chemical, so we would write $E[L; T]$ and $E[X; T]$ where here T stands for level of toxin, past and present. At the moment no attempt is made to represent the dependence of the above means on toxin level in a mechanistic manner, but that is an ultimate objective.

Groups of Cells; (Sub) Organs

Suppose there are C pairs of cells in an organ, with pairs behaving as discussed, and independently cycling between states. Then standard limit theory suggests that if $D(t)$ represents the number of pairs totally differentiated cells present in the organ at time t,

$$Z_D(t) = \frac{D(t) - (Cp_D)}{\sqrt{(C)p_D(1-p_D)}} \tag{3.7}$$

is approximately normal/Gaussian distributed for large C. Divide numerator and denominator of the r h s by C to conclude that as C becomes large the concentration of functional cells $D(t)/C$ approaches a constant (in this case) i.e. p_D.

Model D.2. **A Differential Equation Representation of Cell-Toxin Interaction.**

Let $D(t)$ represent the random number of cell pairs that are in total differentiated state at time t, and $M(t)$ be the number of (potential) pairs undergoing mitosis; $D(t) + M(t) = C$, a constant representing the number of cell pairs in the organ. Suppose the process $\{D(t), t \geq 0\}$ is Markov with generator defined by

$$\begin{aligned} P\{D(t+dt) = D(t)+1 | D(t)\} &= \mu(T)(C - D(t))dt + o(dt) \\ P\{D(t+dt) = D(t)-1 | D(t)\} &= \lambda(T)D(t)dt + o(dt) \end{aligned} \tag{3.8}$$

Then if T is a constant level of toxicity in the system one can take expectations throughout to obtain a linear differential equation for $\overline{D}(t) = E[D(t)]$ the mean of $D(t)$:

$$\frac{d\overline{D}}{dt} = \mu(T)\cdot C - (\mu(T)+\lambda(T))\overline{D}(t); \tag{3.9}$$

the solution of which is

$$\overline{D}(t) = \overline{D}(0)e^{-(\mu(T)+\lambda(T))t} + \frac{C\mu(T)}{\mu(T)+\lambda(T)}\left(1-e^{-(\mu(T)+\lambda(T))t}\right) \tag{3.10}$$

Hence the long-run expected number of totally differentiated pairs is

$$\lim_{t\to\infty}\overline{D}(t) = \frac{C\mu(T)}{\mu(T)+\lambda(T)} \tag{3.11}$$

which bears close resemblance to Model 1 in the long run, expression (3.6), with $\mu(T)^{-1} = E[X]$ and $\lambda(T)^{-1} = E[L]$. For the above model it is again easily seen that (a scaled version of) $D(t)$ is approximately Normal for large C.

Cell-Toxin Interaction

The above motivates the following deterministic differential equation formulation. We allow (3.9) to become

$$\begin{aligned}\frac{d\overline{D}}{dt} &= \mu(\overline{T}(t))C - (\mu(\overline{T}(t)) + \lambda(\overline{T}(t)))\overline{D}(t) \\ \frac{d\overline{T}(t)}{dt} &= \tau(t) - \upsilon\frac{\overline{D}(t)\overline{T}(t)}{1+\kappa\overline{T}(t)}\end{aligned} \tag{3.12}$$

The differential equation for $\overline{T}(t)$, roughly interpretable as the mean concentration of toxin present at t, expresses the fact that the increase in toxin present at t equals the rate of input of toxin minus the rate of output; the latter rate is modeled as a saturated (Michaelis-Menten type) service rate, $\upsilon\overline{T}(t)/(1+\kappa\overline{T}(t))$, multiplied by the concentration of totally differentiated cells in the fluid. In a later section we study a complete probabilistic version of (3.12).

It is perhaps natural, but is conjectural, to attribute functional dependence of the cell-change rates in a way that tends to reduce the rate of increase of functional cells, the "toxin fighters", with toxin concentration. For example (only), let

$$\mu(T) = \mu_0 e^{-\xi T}; \quad \lambda(T) = \lambda_0 e^{\eta T} \tag{3.13}$$

where ξ and η are positive. This choice tends to kill more cells as T increases but to increase the number undergoing mitosis since the duration of the mitotic period is increased. Another possibility is that the *condition* of cells emerging from mitosis is changed in the presence of a toxin: some such cells are deficient, perhaps leading to birth defects, or others become initiated for cancer. We do not now model these many options. Supposing $\tau(t) = \tau$, a constant, the long-run toxin concentration is the solution of

$$\overline{D} = \frac{C\mu(\overline{T})}{\mu(\overline{T}) + \lambda(\overline{T})} \tag{3.14}$$

and

$$\tau = \upsilon \frac{\overline{D}\,\overline{T}}{1 + \kappa\overline{T}} = \frac{\upsilon C \mu(\overline{T})\overline{T}}{(1 + \kappa\overline{T})\left[\mu(\overline{T}) + \lambda(\overline{T})\right]}$$

or (3.15)

$$\tau = \frac{\upsilon C \mu_0 \overline{T}}{(1 + \kappa\overline{T})\left[\mu_0 + \lambda_0 e^{(\xi+\eta)\overline{T}}\right]}$$

A graph shows that a finite steady-state long-run solution for toxin level, namely $\overline{T}$, will exist under certain conditions. Note that in Fig. 1 two solutions to (3.15) can exist.

If

$$\tau < \max_{\overline{T}} \left(\frac{\upsilon C \mu_0 \overline{T}}{(1 + \kappa\overline{T})\left[\mu_0 + \lambda_0 e^{(\xi+\eta)\overline{T}}\right]} \right).$$

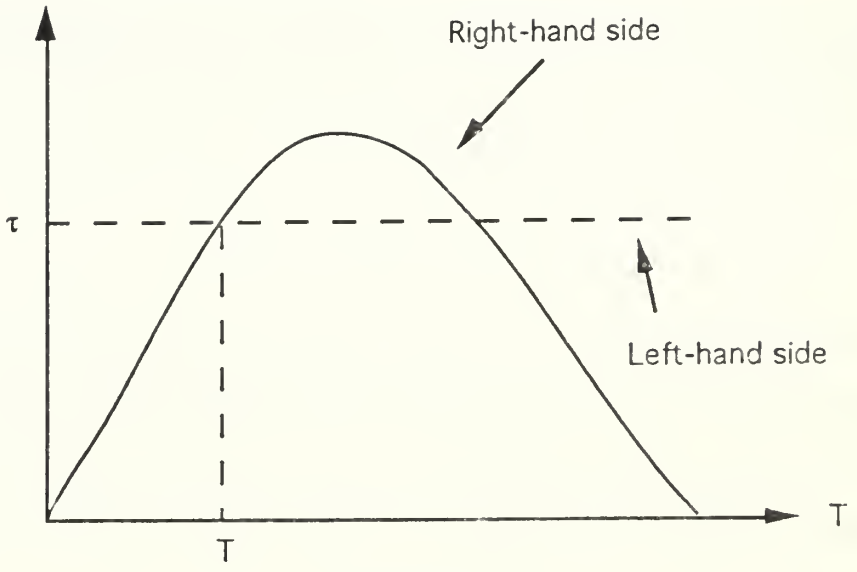

Figure 1

It seems clear that the smaller of the two possible solutions is biologically plausible, since it is evidently an increasing function of τ, whereas the other solution decreases. If the above inequality is not satisfied the organ is soon overcome and toxin concentration increases indefinitely.

Model D.3. **A Cell-Age-Specific Differential Equation Model of Cell-Toxin Interaction: The Effects of Apoptosis and Necrosis.**

In order to model the effects of programmed cell death or *apoptosis*, and death from insult, called *necrosis*, it is necessary to represent the cell-aging phenomenon. We choose to do this in the context of Markov chains or rate equations, simply extending (3.12), by the consideration of two totally differentiated cell types: *new* or young, namely those that have comparatively recently been "born", i.e., emerged from mitosis, and *old*, those that have transitioned from the new state ("reached maturity") and are now eligible to die.

The following rate equations reflect the effects of a toxin in the above process. Let $D_n(t)$ be the number of *new* or young cell pairs (recently emerged from

mitosis), $D_0(t)$ the number of *old* cell pairs, and $T(t)$ the amount of toxin in contact with them. Then we write

$$\frac{d\overline{D}_n(t)}{dt} = -\lambda_n\left(e^{\eta_n\overline{T}(t)} - 1\right)\overline{D}_n(t) - \phi\overline{D}_n(t)$$
$$+\mu e^{-\xi T(t)}\left(C - \overline{D}_n(t) - \overline{D}_0(t)\right) \tag{3.16}$$

$$\frac{d\overline{D}_0(t)}{dt} = -\lambda_0 e^{\eta_0 T(t)}\overline{D}_0(t) + \phi\overline{D}_n(t) \tag{3.17}$$

$$\frac{d\overline{T}(t)}{dt} = \tau(t) - \frac{\upsilon_n\overline{T}(t)\overline{D}_n(t)}{1+\kappa_n\overline{T}(t)} - \frac{\upsilon_0\overline{T}(t)\overline{D}_0(t)}{1+\kappa_0\overline{T}(t)} \tag{3.18}$$

Consider first (3.16). The first term on the right-hand side represents a death rate of new cell pairs that increases with toxin concentration and is zero with none. It represents the effect of toxin-induced *necrosis* upon the new cell pairs. The second term is an aging term: it represents the rate at which new cells enter the old-cell population. The third term represents the mitosis rate; mitosis resembles birth in that new cell pairs are the product. It has been assumed that mitosis rate always decreases with increased toxin concentration, but such need not be the case.

Next, consider (3.17). The first term is a death rate for old cell pairs that increases with toxin concentration; it represents both *necrosis* and *apoptosis*. The second term is the rate of maturation of new cells into old. Doubtless the transition rate, ϕ, could depend upon toxicity in the organ, but this possible dependence is not modeled here. Biological insight and information can perhaps suggest an appropriate and interesting functional dependence for ϕ.

Finally, (3.18) models the rate of toxin concentration increase. The first term is the rate at which the basic toxin reaches the vicinity of the cells. The second and

third terms both represent the rates at which toxin concentration is reduced by action of new cells (second term) and old cells (third term). Note that both cell types reduce toxin concentration roughly in proportion to that concentration, but their effects saturate *a la* Michaelis-Menton.

The equations supplied are illustrative of what *may* happen for certain toxins and cell types; they are intended to provoke discussion and stimulate experimental and observational checking and revision.

A steady-state solution to equations (3.16) – (3.18) for a constant toxin input $\tau(t) \equiv \tau$ would satisfy

$$0 = -\lambda_n\left(e^{\eta_n T} - 1\right)D_n - \phi D_n + \mu e^{-\xi T}\left(C - D_n - D_0\right) \tag{3.16a}$$

$$0 = -\lambda_0 e^{\eta_0 T} D_0 + \phi D_n \tag{3.17a}$$

$$0 = \tau - \frac{\upsilon_n T D_n}{1 + \kappa_n T} - \frac{\upsilon_0 T D_0}{1 + \kappa_0 T} \tag{3.18a}$$

Simplification of (3.16a) – (3.17a) results in

$$D_0 = \frac{\phi}{\lambda_0} e^{-\eta_0 T} D_n \tag{3.19}$$

$$D_n = \mu_0 e^{-\xi T} C \times \left[\lambda_n\left(e^{\eta_n T} - 1\right) + \phi + \mu e^{-\xi T}\left(1 + \frac{\phi}{\lambda_0} e^{-\eta_0 T}\right)\right]^{-1} \tag{3.20}$$

Finally, expressions (3.19) – (3.20) can be substituted into equation (3.18a) to obtain an equation for T. This latter equation can have 0, 1 or 2 solutions. If it has no solutions, then $D_n = D_0 = 0$ and the organ is dead. If the equation has two solutions, then the smaller of the two possible solutions T_s is biologically plausible since the smaller solution is an increasing function of τ, whereas the larger solution is a decreasing function.

If $\tau = 0$, then $T = 0$ and

$$D_n = \frac{\mu}{\phi + \mu\left(1 + \frac{\phi}{\lambda_0}\right)} \tag{3.21}$$

$$D_0 = \left(\frac{\phi}{\lambda_0}\right)\frac{\mu}{\left[\phi + \mu\left(1 + \frac{\phi}{\lambda_0}\right)\right]} \tag{3.22}$$

4. Numerical Illustrations.

We have submitted the above hypothetical equations to several dosage regimes.

Illustration 1.

Suppose toxin input is 0 until time $t = 5$, after which a constant exposure τ is given. Figure 1 displays the function

$$f(T) = \frac{\upsilon_n T D_n}{1 + \kappa_n T} + \frac{\upsilon_0 T D_0}{1 + \kappa_0 T}$$

where D_n and D_0 are obtained from equation (3.19) and (3.20); the parameter values used are displayed on the figure. The (possible) solution(s) to equation (3.18a) can be found drawing a horizontal line at the value of τ of interest. The limiting amount of toxin in the organ subject to a constant input of toxin τ is the smaller of the two values of T corresponding to the intersection points of f with the horizontal line. Note that there is no solution for $\tau > 3.53$, the maximum value of the function. This means that toxin has killed all old and new cells; long before that occurs the organism has died.

Figures 2–5 display the results of a numerical solution of equation (3.16)–(3.18) for values of $\tau = 0$, 1, 2, 3, 3.3, and 3.53. The other parameter values used

are displayed on the Figures. The initial values of the numbers of young and old cell pairs and the amount of toxin present are the limiting values when $\tau = 0$.

Figure 2 shows the effects of various *levels of toxin* on the young cell pair population. At the beginning of exposure the young cell population decreases. However, if the level of toxin is not too large, after this initial decrease the young cell population increases to a limiting value higher than that occurring when $\tau = 0$. If the level of exposure is too high, the young cell population decreases to zero.

Figure 3 shows the effects of various levels of toxin on the old cell pair population. If the level of exposure is too high, the old cell population decreases to 0. For low or moderate exposure levels the old cell population initially decreases but then recovers somewhat to a limiting value which is below the limiting value if there were no toxin.

Figure 4 displays the total number of totally differentiated cell pairs. As the level of exposure increases the total number of cell pairs decreases. The total number of totally differentiated cell pairs initially decreases, then recovers somewhat before decreasing a little again to a limiting value.

Figure 5 displays the level of toxin in the organ.

It seems possible that our model represents an effect called hormesis wherein a smallish amount of deleterious agent induces a biological entity to over-compensate for a (low-level) insult, but eventually to succumb to a larger dose. If young cells are actually more efficient and productive than old then the proportional buildup of the new-cell population for low toxin levels has just such an effect *in our example.*

5. Stochastic Versions of Models

The purpose of this section is to describe a fully stochastic version of the cell-toxin interaction. Note that once stochastic elements are permitted to enter a great many optional behaviors can be modeled. It will be seen that expressions (3.12), (3.16), (3.17), and (3.18) are not exact replicas of the correct mean or expected-value equations.

Model S.1. *Markovian Model* of Cell-Toxin Interaction.

Suppose $D(t)$ represents the number of totally differentiated cell pairs in an organ with a maximum of C pairs, and $T(t)$ is the toxin concentration at time t. Both $D(t)$ and $T(t)$ are now considered to vary randomly.

Let $(D(t), T(t),\ t \geq 0)$ be a bivariate birth and death Markov process in continuous time and with state space $R \times R$, i.e., all pairs of integers such that $0 \leq D(t) \leq C$, $0 \leq T(t)$. Then put for the transition probabilities from $t \rightarrow t + \Delta$

$$P\{(D(t+\Delta),T(t+\Delta)) = (D(t)+1,T(t)) | D(t),T(t)\} = \mu(T(t))(C - D(t))\Delta + o(\Delta)$$

$$P\{(D(t+\Delta),T(t+\Delta)) = (D(t)-1,T(t)) | D(t),T(t)\} = \lambda(T(t))D(t)\Delta + o(\Delta)$$

$$P\{(D(t+\Delta),T(t+\Delta)) = (D(t),T(t)+1) | D(t),T(t)\} = \tau(t)\Delta + o(\Delta)$$

$$P\{(D(t+\Delta),T(t+\Delta)) = (D(t),T(t)-1) | D(t),T(t)\} = \upsilon\frac{D(t)T(t)}{1+\kappa T(t)}\Delta + o(\Delta)$$

$$P\{(D(t+\Delta),T(t+\Delta)) = (D(t),T(t)) | D(t),T(t)\} = 1 - p(D(t),T(t))\Delta + o(\Delta), \qquad (5.1)$$

where $p(D(t),T(t)) = \mu(T(t))(C - D(t)) + \lambda(T(t))D(t) + \tau(t) + \upsilon D(t)T(t) / (1 + \kappa T(t))$; $1-p\Delta$ is simply the probability of no change in the time period $(t, t + \Delta)$.

Examination of (5.1) reveals that, under very special conditions, expected-value and higher-moment equations can be written down, and can be solved numerically. Non-linearities in general impede such a step, but approximation

and perturbation methodologies can be invoked to produce useful approximations.

The Mean Equations

Invoke (5.1) to obtain

$$\begin{aligned} E\left[D(t+\Delta)\middle|D(t),T(t)\right] &= (D(t)+1)\mu(T(t))(C-D(t))\Delta \\ &\quad +(D(t)-1)\lambda(T(t))D(t)\Delta \\ &\quad +D(t)\left[1-\mu(T(t))(C-D(t))\Delta-\lambda(T(t))D(t)\Delta\right]+o(\Delta) \\ &= \mu(T(t))(C-D(t))\Delta-\lambda(T(t))D(t)\Delta+D(t)+o(\Delta). \end{aligned} \tag{5.2}$$

Hence, upon removing the condition and passing to the limit

$$\boxed{\frac{d}{dt}E[D(t)] = E\left[\mu(T(t))\right]C - E\left[D(t)\mu(T(t))\right] - E\left[\lambda(T(t))D(t)\right]} \tag{5.3}$$

Next,

$$\begin{aligned} E\left[T(t+\Delta)\middle|D(t),T(t)\right] &= (T(t)+1)\tau(t)\Delta+(T(t)-1)\upsilon\frac{D(t)T(t)}{1+\kappa T(t)}\Delta \\ &\quad +T(t)\left[1-\left(\tau(t)\Delta+\upsilon\frac{D(t)T(t)}{1+\kappa T(t)}\Delta\right)\right]. \end{aligned}$$

Removal of the condition leads to

$$\boxed{\frac{d}{dt}E[T(t)] = \tau(t)-\upsilon E\left[\frac{D(t)T(t)}{1+\kappa T(t)}\right].} \tag{5.4}$$

These *resemble* the previously-presented deterministic model (3.12), but only roughly, since expectations of non-linear functions such as appear above cannot be directly evaluated. Special methods can be used that give satisfactory approximations.

Clearly the equations (5.3) and (5.4) cannot be solved without the introduction of approximate equations for the non-linear expectations on the r h s. One approach for doing this is presented in Appendix A. A second approach is presented in the next section.

Asymptotics for C Large.

Since the number of cells in an organ, C, is large, being of order 10^7, it is natural to consider explicit asymptotic approximations based on that fact. In what follows we proceed formally. For precedent here see McNeil and Schach (1973) but also more recent work.

Define the joint moment generating function (assumed to exist), to be

$$\Psi(\theta_d,\theta_t;t)\overset{(d)}{=}E\left[e^{\theta_d D(t)+\theta_t T(t)}\right]. \tag{5.5}$$

Use the Markov property to derive forward equations in transform space:

$$E\left[e^{\theta_d D(t+\Delta)+\theta_t T(t+\Delta)}\middle|D(t),T(t)\right]=$$

$$e^{\theta_d(D(t)+1)+\theta_t T(t)}\mu(T(t))(C-D(t))\Delta+e^{\theta_d(D(t)-1)+\theta_t T(t)}\lambda(T(t))D(t)\Delta$$

$$+e^{\theta_d D(t)+\theta_t(T(t)+1)}\tau(t)\Delta+e^{\theta_d D(t)+\theta_t(T(t)-1)}\frac{\upsilon D(t)T(t)\Delta}{1+\kappa T(t)}$$

$$+e^{\theta_d D(t)+\theta_t T(t)}\left[1-p(D(t),T(t))\Delta\right]+o(\Delta),$$

where

$$p(D(t),T(t))=\mu(T(t))(C-D(t))+\lambda(T(t))D(t)+\tau(t)+\frac{\upsilon D(t)T(t)}{1+\kappa T(t)}.$$

Thus

$$E\left[e^{\theta_d D(t+\Delta)+\theta_t T(t+\Delta)}\right] \equiv \Psi(\theta_d, \theta_t; t+\Delta)$$

$$= E\left[e^{\theta_d D(t)+\theta_d+\theta_t T(t)}\mu(T(t))(C-D(t))\Delta\right]$$

$$+E\left[e^{\theta_d D(t)-\theta_d+\theta_t T(t)}\lambda(T(t))D(t)\Delta\right]$$

$$+E\left[e^{\theta_d D(t)+\theta_t T(t)+\theta_t}\tau(t)\Delta\right]+E\left[e^{\theta_d D(t)+\theta_t T(t)-\theta_t}\frac{\upsilon D(t)T(t)}{1+\kappa T(t)}\Delta\right]$$

$$+E\left[e^{\theta_d D(t)+\theta_t T(t)}\right]-E\left[e^{\theta_d D(t)+\theta_t T(t)}p(D(t),T(t))\right] \qquad (5.6)$$

Consequently, after re-arrangement and division by Δ, and letting $\Delta \to 0$,

$$\frac{d\Psi(\theta_d,\theta_t)}{dt} = \left(e^{\theta_d}-1\right)E\left[e^{\theta_d D(t)+\theta_t T(t)}\mu(T(t))(C-D(t))\right]$$

$$+\left(e^{-\theta_d}-1\right)E\left[e^{\theta_d D(t)+\theta_t T(t)}\lambda(T(t))D(t)\right]$$

$$+\left(e^{\theta_t}-1\right)E\left[e^{\theta_d D(t)+\theta_t T(t)}\right]\tau(t)$$

$$+\upsilon(t)\left(e^{-\theta_t}-1\right)E\left[e^{\theta_d D(t)+\theta_t T(t)}\frac{D(t)T(t)}{1+\kappa T(t)}\right]. \qquad (5.7)$$

These equations are highly non-linear and intractable; consequently we introduce an appropriate asymptotic analysis that assumes C, the number of cell pairs, to be large.

Scaling

Define

$$X(t) = \frac{D(t)-C\,\alpha(t)}{\sqrt{C}},\quad Y(t) = \frac{T(t)-C\beta(t)}{\sqrt{C}} \qquad (5.8)$$

and the joint mgf of the scaled "noise" variables $X(t)$ and $Y(t)$:

$$\varphi(\theta_d,\theta_t;t)\overset{(d)}{=}E\left[e^{\theta_d X(t)+\theta_t Y(t)}\right]$$

$$=E\left[e^{\theta_d D(t)/\sqrt{C}+\theta_t T(t)/\sqrt{C}}\right]e^{-\left(\theta_d\sqrt{C}\alpha(t)+\theta_t\sqrt{C}\beta(t)\right)}$$

$$=\Psi\left(\theta_d/\sqrt{C},\theta_t/\sqrt{C},t\right)e^{-\sqrt{C}(\theta_d\alpha(t)+\theta_t\beta(t))} \tag{5.9}$$

Consequently,

$$\Psi\left(\theta_d/\sqrt{C},\theta_t/\sqrt{C},t\right)=\varphi(\theta_d,\theta_t;t)e^{\sqrt{C}(\theta_d\alpha(t)+\theta_t\beta(t))}. \tag{5.10}$$

It is necessary to find equations for $\alpha(t)$ and $\beta(t)$, and the joint mgf $\varphi(\theta_d, \theta_t; t)$.

Proceed as follows:

use (5.7); re-define the transform variables as below $\theta_d \to \theta_d/\sqrt{C}$, $\theta_t \to \theta_t/\sqrt{C}$;

from (5.10) we get

$$\frac{d\Psi}{dt}\left(\theta_d/\sqrt{C},\theta_t/\sqrt{C};t\right)=\frac{d\varphi}{dt}e^{\sqrt{C}(\theta_d\alpha(t)+\theta_t\beta(t))}+\varphi\sqrt{C}\left(\theta_d\alpha'(t)+\theta_t\beta'(t)\right)e^{\sqrt{C}(\theta_d\alpha(t)+\theta_t\beta(t))}$$

$$=E\Bigg[e^{\left(\theta_d/\sqrt{C}\right)\left(\sqrt{C}X(t)+C\alpha(t)\right)}e^{\left(\theta_t/\sqrt{C}\right)\left(\sqrt{C}Y(t)+C\beta(t)\right)}$$

$$\times\Bigg\{\left(e^{\theta_d/\sqrt{C}}-1\right)\left(\mu\left(C\beta(t)+\sqrt{C}Y(t)\right)\left(C-C\alpha(t)-\sqrt{C}X(t)\right)\right)$$

$$+\left(e^{-\theta_d/\sqrt{C}}-1\right)\left(\lambda\left(C\beta(t)+\sqrt{C}Y(t)\right)\left(C\alpha(t)-\sqrt{C}X(t)\right)\right)$$

$$+\left(e^{\theta_t/\sqrt{C}}-1\right)\tau(t)$$

$$+\upsilon(t)\left(e^{-\theta_t/\sqrt{C}}-1\right)\frac{\left(C\alpha(t)+\sqrt{C}X(t)\right)\left(C\beta(t)+\sqrt{C}Y(t)\right)}{1+\kappa\left(C\beta(t)+\sqrt{C}Y(t)\right)}\Bigg\}\Bigg]. \tag{5.11}$$

Next scale the transition rates

$$\mu\left(C\beta(t)+\sqrt{C}Y(t)\right)=\mu^*\left(\beta(t)+Y(t)/\sqrt{C}\right) \tag{5.12a}$$

$$\lambda\left(C\beta(t)+\sqrt{C}Y(t)\right)=\lambda^*\left(\beta(t)+Y(t)/\sqrt{C}\right) \tag{5.12b}$$

$$\upsilon(t) = \upsilon^*(t)/C \qquad \tau(t) = C\tau^*(t) \tag{5.12c}$$

$$\kappa\left(C\beta(t) + \sqrt{C}Y(t)\right) = \kappa^*\left(\beta(t) + Y(t)/\sqrt{C}\right) \tag{5.12d}$$

in order to obtain non-degenerate results involving all aspects of the process as C becomes large. Starred functions or parameters are $O(1)$.

Expand state-dependent parameters by Taylor series in powers of $1/\sqrt{C}$ after cancelling $e^{\sqrt{C}(\theta_d\alpha(t)+\theta_t\beta(t))}$ from both sides; we put $\mu_0^*(\beta(t))$ for the first term of the expansion of $\mu^*\left(\beta(t)+Y(t)/\sqrt{C}\right)$; notation for λ^* and κ^* is analogous. We obtain

$$\frac{\partial\varphi}{\partial t} + \varphi\sqrt{C}\left(\theta_d\alpha'(t) + \theta_t\beta'(t)\right) =$$

$$E\Bigg[e^{\theta_d X(t)}e^{\theta_t Y(t)} \times \Bigg\{\left(\frac{\theta_d}{\sqrt{C}} + \frac{\theta_d^2}{2C} + \ldots\right)\left(\mu_0^*(\beta(t)) + \mu_1^*(\beta(t))\cdot\frac{Y(t)}{\sqrt{C}}\ldots\right)\left(C - C\alpha(t) - \sqrt{C}X(t)\right)$$

$$+\left(-\frac{\theta_d}{\sqrt{C}} + \frac{\theta_d^2}{2C} + \ldots\right)\left(\lambda_0^*(\beta(t)) + \lambda_1^*(\beta(t))\cdot\frac{Y(t)}{\sqrt{C}}\ldots\right)\left(C\alpha(t) + \sqrt{C}X(t)\right)$$

$$+\left(\frac{\theta_t}{\sqrt{C}} + \frac{\theta_t^2}{2C} + \ldots\right)C\tau^*(t)$$

$$+\left(-\frac{\theta_t}{\sqrt{C}} + \frac{\theta_t^2}{2C} + \ldots\right)\upsilon^*(t)/C\,\frac{\left(C\alpha(t) + \sqrt{C}X(t)\right)\left(C\beta(t) + \sqrt{C}Y(t)\right)}{1 + \kappa_0^*(\beta(t)) + \kappa_1^*(\beta(t))Y(t)/\sqrt{C}}\Bigg\}\Bigg]. \tag{5.13}$$

Re-write the last line above in expanded form to get

$$\left(-\frac{\theta_t}{\sqrt{C}} + \frac{\theta_t^2}{2C} + \ldots\right)\upsilon^*(t)\left(\alpha(t) + X(t)/\sqrt{C} + \ldots\right)\left(\beta(t) + Y(t)/\sqrt{C} + \ldots\right)C\frac{1}{1 + \kappa_0^*(\beta(t))} \times$$

$$\left(1 - \left(\kappa_1^*(\beta(t))/\left(1 + \kappa_0^*(\beta(t))\right)\right)\frac{Y(t)}{\sqrt{C}} + \ldots\right) \tag{5.14}$$

$$\frac{\partial\varphi}{\partial t}+\sqrt{C}\left(\theta_d\alpha'(t)+\theta_t\beta'(t)\right)\varphi=$$

$$\left\{\left(\frac{\theta_d}{\sqrt{C}}+\frac{\theta_d^2}{2C}+\ldots\right)C\left(\mu_0^*(t)(1-\alpha(t))\varphi+\mu_1^*(t)(1-\alpha(t))\frac{1}{\sqrt{C}}\frac{\partial\varphi}{\partial\theta_t}-\mu_0^*(t)\frac{1}{\sqrt{C}}\frac{\partial\varphi}{\partial\theta_d}+\ldots\right)\right.$$

$$+\left(-\frac{\theta_d}{\sqrt{C}}+\frac{\theta_d^2}{2C}\right)C\left(\lambda_0^*(t)\alpha(t)\varphi+\lambda_1^*(t)\alpha(t)\frac{1}{\sqrt{C}}\frac{\partial\varphi}{\partial\theta_t}+\lambda_0^*(t)\frac{1}{\sqrt{C}}\frac{\partial\varphi}{\partial\theta_d}+\ldots\right)$$

$$+\left(\frac{\theta_t}{\sqrt{C}}+\frac{\theta_t^2}{2C}+\ldots\right)C\varphi\tau^*(t)$$

$$+\left(-\frac{\theta_t}{\sqrt{C}}+\frac{\theta_t^2}{2C}+\ldots\right)C\left(\upsilon^*(t)\frac{\alpha(t)\beta(t)}{1+\kappa_0^*(t)}\varphi+\left(\left(\frac{\upsilon^*(t)\beta(t)}{1+\kappa_0^*(t)}\right)\frac{1}{\sqrt{C}}\frac{\partial\varphi}{\partial\theta_d}+\ldots\right)\right.$$

$$\left.\left.+\upsilon^*(t)\frac{\alpha(t)}{1+\kappa_0^*(t)}\frac{1}{\sqrt{C}}\frac{\partial\varphi}{\partial\theta_t}-\upsilon^*(t)\frac{\alpha(t)\beta(t)\kappa_1^*(t)}{\left(1+\kappa_0^*(t)\right)^2}\frac{1}{\sqrt{C}}\frac{\partial\varphi}{\partial\theta_t}+\ldots\right)\right\} \tag{5.15}$$

We express the dependence of φ on C as follows:

$$\varphi(\theta_d,\theta_t;t,C)=\varphi_0(\theta_d,\theta_t;t)+\varphi_1(\theta_d,\theta_t;t)\frac{1}{\sqrt{C}}+\ldots \tag{5.16}$$

Now substitute into (5.15) to obtain

$$\sum_{j=0}^{\infty}\frac{\partial\varphi_j}{\partial t}\left(\frac{1}{\sqrt{C}}\right)^j+\sqrt{C}\left(\theta_d\alpha'(t)+\theta_t\beta'(t)\right)\sum_{j=0}^{\infty}\varphi_j\left(\frac{1}{\sqrt{C}}\right)^j=$$

$$\left\{\left(\frac{\theta_d}{\sqrt{C}}+\frac{\theta_d^2}{2C}+\ldots\right)C\left(\mu_0^*(t)(1-\alpha(t))\sum_{j=0}^{\infty}\varphi_j\left(\frac{1}{\sqrt{C}}\right)^j+\mu_1^*(t)(1-\alpha(t))\frac{1}{\sqrt{C}}\sum_{j=0}^{\infty}\frac{\partial\varphi_j}{\partial\theta_t}\frac{1}{\left(\sqrt{C}\right)^j}\right.\right.$$

$$\left.-\mu_0^*(t)\frac{1}{\sqrt{C}}\sum_{j=0}^{\infty}\frac{\partial\varphi_j}{\partial\theta_d}\frac{1}{\left(\sqrt{C}\right)^j}+\ldots\right)$$

$$+\left(-\frac{\theta_d}{\sqrt{C}}+\frac{\theta_d^2}{2C}+\ldots\right)C\left(\lambda_0^*(t)\alpha(t)\sum_{j=0}^{\infty}\varphi_j\frac{1}{\left(\sqrt{C}\right)^j}+\lambda_1^*(t)\alpha(t)\frac{1}{\sqrt{C}}\sum_{j=0}^{\infty}\frac{\partial\varphi_j}{\partial\theta_t}\frac{1}{\left(\sqrt{C}\right)^j}\right.$$

$$\left.+\lambda_0^*(t)\frac{1}{\sqrt{C}}\sum_{j=0}^{\infty}\frac{\partial\varphi_j}{\partial\theta_d}\frac{1}{\left(\sqrt{C}\right)^j}+\ldots\right) \qquad (5.17)$$

$$+\left(\frac{\theta_t}{\sqrt{C}}+\frac{\theta_t^2}{2C}+\ldots\right)C\tau^*(t)\sum_{j=0}^{\infty}\varphi_j\frac{1}{\left(\sqrt{C}\right)^j}$$

$$+\left(-\frac{\theta_t}{\sqrt{C}}+\frac{\theta_t^2}{2C}+\ldots\right)C\left(\upsilon^*(t)\frac{\alpha(t)\beta(t)}{1+\kappa_0^*(t)}\sum_{j=0}^{\infty}\varphi_j\frac{1}{\left(\sqrt{C}\right)^j}\right.$$

$$+\frac{\upsilon^*(t)\beta(t)}{1+\kappa_0^*(t)}\frac{1}{\sqrt{C}}\sum_{j=0}^{\infty}\frac{\partial\varphi_j}{\partial\theta_d}\frac{1}{\left(\sqrt{C}\right)^j}$$

$$\left.\left.+\frac{\upsilon^*(t)\alpha(t)}{1+\kappa_0^*(t)}\left[1-\frac{\beta(t)\kappa_1^*(t)}{1+\kappa_0^*(t)}\right]\frac{1}{\sqrt{C}}\sum_{j=0}^{\infty}\frac{\partial\varphi_j}{\partial\theta_t}\frac{1}{\left(\sqrt{C}\right)^j}+\ldots\right)\right\}$$

where the omitted terms ("...") are $O(1/C)$, and $\lambda_0^*(t)\equiv\lambda_0^*(\beta(t))$ etc.

Identify terms of order $\sqrt{C}$:

l h s: $(\theta_d \alpha'(t) + \theta_t \beta'(t))\varphi_0$ (5.18a)

r h s: $\theta_d\left[\left(\mu_0^*(\beta(t))(1-\alpha(t))\right) - \alpha(t)\lambda_0^*(\beta(t))\right]\varphi_0 + \theta_t\left[\tau^*(t) - \frac{\upsilon^*(t)\alpha(t)\beta(t)}{1+\kappa_0^*(\beta(t))}\right]\varphi_0$; (5.18b)

since these must cancel, the functions $\alpha(t)$ and $\beta(t)$ satisfy the differential equations

$$\alpha'(t) = \mu_0^*(\beta(t))(1-\alpha(t)) - \lambda_0^*(\beta(t))\alpha(t)$$

$$\beta'(t) = \tau^*(t) - \upsilon^*(t)\frac{\alpha(t)\beta(t)}{1+\kappa_0^*(\beta(t))} \qquad (5.19)$$

the latter must in general be solved numerically, but steady-state information can be derived more easily. The system of equations (5.19) is a scaled version of equation (3.12).

Next, identify terms of order 1 (coefficient of $\left(1/\sqrt{C}\right)^0$. The expression obtained is of the form

$$\frac{\partial \varphi_0}{\partial t} = \left(\frac{\theta_d^2}{2}A_d(t) + \frac{\theta_t^2}{2}A_t(t)\right)\varphi_0$$
$$+B_{dd}(t)\theta_d\frac{\partial \varphi_0}{\partial \theta_d} + B_{dt}(t)\theta_t\frac{\partial \varphi_0}{\partial \theta_d}$$
$$+B_{td}(t)\theta_d\frac{\partial \varphi_0}{\partial \theta_t} + B_{tt}(t)\theta_t\frac{\partial \varphi_0}{\partial \theta_t}. \qquad (5.20)$$

Here the above coefficients are

$$A_d(t) = \left(\mu_0^*(t)(1-\alpha(t)) + \lambda_0^*(t)\alpha(t)\right) \tag{5.21a}$$

$$A_t(t) = \left(\tau^*(t) + \frac{\upsilon^*(t)\alpha(t)\beta(t)}{1+\kappa_0^*(t)}\right) \tag{5.21b}$$

$$B_{dd}(t) = -\mu_0^*(t) - \lambda_0^*(t) \tag{5.21c}$$

$$B_{dt}(t) = -\frac{\upsilon^*(t)\beta(t)}{1+\kappa_0^*(t)} \tag{5.21d}$$

$$B_{td}(t) = \mu_1^*(t)(1-\alpha(t)) - \lambda_1^*(t)\alpha(t) \tag{5.21e}$$

$$B_{tt}(t) = -\frac{\upsilon^*(t)\alpha(t)}{1+\kappa_0^*(t)}\left[1 - \frac{\beta(t)\kappa_1^*(t)}{1+\kappa_0^*(t)}\right]. \tag{5.21f}$$

The resulting partial differential equation for φ_0 is recognizable as characterizing the joint mgf of an Ornstein-Uhlenbeck (Gaussian) stochastic process.

Moment Equations.

Differentiation of the pde with respect to θ_d and θ_t allows recovery of differential equations for the covariance function of $(X(t), Y(t))$, the scaled stochastic terms describing deviations from the mean (to order C) term

$$E[D(t)] \cong C\alpha(t),\ E[T(t)] \cong C\beta(t) \tag{5.22}$$

Differentiation of $\varphi_0(\theta_d, \theta_t; t)$ at $\theta_d = \theta_t = 0$ shows first that if $X(0) = Y(0)$, then $E[X(t)] = E[Y(t)] = 0$ to the order suggested. Second derivatives at $\theta = 0$ then deliver these differential equations for the variances and covariances,

$$Var[X(t)] \equiv E[X^2(t)] = m_{dd}(t), Var[Y(t)] \equiv E[Y^2(t)] = m_{tt}(t) \tag{5.23}$$

$$Cov[X(t), Y(t)] \equiv E[X(t) \cdot Y(t)] = m_{dt}(t), \tag{5.24}$$

$$\frac{d}{dt} m_{dd}(t) = A_d(t) + 2B_{dd}(t) m_{dd}(t) + 2B_{td} m_{dt}(t) \tag{5.25}$$

$$\frac{d}{dt} m_{dt} = (B_{dd}(t) + B_{tt}(t)) m_{dt}(t) + B_{dt}(t) m_{dd}(t) + B_{td} m_{tt}(t) \tag{5.26}$$

$$\frac{d}{dt} m_{tt}(t) = A_t(t) + 2B_{tt}(t) m_{tt}(t) + 2B_{dt} m_{dt}(t). \tag{5.27}$$

These equations can be solved numerically. Owing to the appearance of the Ornstein-Uhlenbeck, Feller (1966), we can argue that for large C, $\boldsymbol{D}(t)$ is approximately normal with mean $C\alpha(t)$ and variance $C\, m_{dd}(t)$; $\boldsymbol{T}(t)$ is asymptotically normal with mean $C\,\beta(t)$ and variance $C\, m_{tt}(t)$; the two quantities are correlated with correlation coefficient $\rho_{dt}(t) = m_{dt}(t) / \sqrt{m_{dd}(t) m_{tt}(t)}$.

Steady-State Solutions: Dose-Response for Steady Exposure

Suppose $\tau^*(t) = \tau^*$, a constant, and that exposure has proceeded for some time so that a steady-state condition has been reached; this is modeled by letting $\alpha'(t) = \beta'(t) = 0$ in (5.19). We have, suppressing t and invoking the tentative working parametric forms (3.13),

$$\mu_0 e^{-\xi^* \beta}(1-\alpha) = \lambda_0 e^{\eta^* \beta} \alpha \tag{5.28a}$$

$$\tau^* = \upsilon^* \frac{\alpha\beta}{1 + \kappa_0^*(\beta)}. \tag{5.28b}$$

Notice that (5.28a) can be solved for β, the steady-state toxin concentration, in terms of α, the steady-state fraction of totally differentiated cells:

$$\beta = \frac{1}{\xi^* + \eta^*} \ln\left(\frac{\mu_0}{\lambda_0}\left(\frac{1-\alpha}{\alpha}\right)\right). \tag{5.29}$$

This can now be inserted into (5.28b) to obtain an implicit *dose-response* relationship:

$$\tau^* = \upsilon^* \frac{\alpha}{1+\kappa_0^*(\beta)} \frac{1}{\left(\xi^* + \eta^*\right)} \ln\left(\frac{\mu_0}{\lambda_0}\left(\frac{1-\alpha}{\alpha}\right)\right); \tag{5.30}$$

the above, (5.30), can be solved for $\alpha[\tau^*]$ so as to depict the fraction of totally differentiated cells' dependence on input toxin; the latter must here be a steady flow.

Slope of Dose-Response Curve for Small Dose.

Of interest to risk analysis is the behavior of the dose response curve for small values of (toxic) dose. We approximate this by finding an expression for $-\frac{d\alpha\left[\tau^*\right]}{d\tau^*}\Big|_{\tau^*=0} = \frac{d}{d\tau^*}\left(1-\alpha\left[\tau^*\right]\right)\Big|_{\tau^*=0}$, the rate of increase of the fraction of non-functioning totally differentiated cells when toxin input is very small.

First notice that if $\tau^* = 0$ then $\mu_0(1-\alpha)/\lambda_0\alpha = 1$. So differentiation of (5.30) at $\tau^* = 0$ provides

$$-\frac{d\alpha\left[\tau^*\right]}{d\tau^*}\Big|_{\tau^*=0} = \left(\frac{\xi^* + \eta^*}{\upsilon^*}\right)\left(1+\kappa_0^*(\beta)\right)\left(1-\alpha[0]\right)$$

$$= \frac{\xi^* + \eta^*}{\upsilon^*}\left(1+\kappa_0^*(\beta)\right)\frac{\mu_0}{\mu_0+\lambda_0} \quad . \tag{5.31}$$

Another differentiation will give information concerning the curvatures of the response, or propensity to exhibit "hockey-stick" or knee-like or threshold behavior at small dose levels. A knowledge of such behavior is of interest to toxicologists and regulators who are concerned with risks in the workplace. It will be kept in mind that the behavior elucidated depends to an unknown degree upon the suitability of the models.

Model S.2. *Markovian Model* of Cell-Age-Specific Cell-Toxin Interaction.

Suppose $D_n(t)$ represents the number of young (or new) cell pairs (recently emerged from mitosis), $D_o(t)$ the number of old cell pairs, and $T(t)$ is the toxin concentration at time t. All the variables $D_n(t)$, $D_o(t)$ and $T(t)$ are now considered to vary randomly.

Let $(D_o(t),\ D_n(t),\ T(t);\ t \geq 0)$ be a trivariate birth and death process in continuous time and with state space $R \times R \times R$, i.e., all triples of integers such that $0 \leq D_o(t) + D_n(t) \leq C$, $0 \leq T(t)$. Then, put for the transition probabilities from $t \rightarrow t + \Delta$.

$$P\{(D_o(t+\Delta), D_n(t+\Delta), T(t+\Delta)) = (D_o(t)+1, D_n(t)-1, T(t)) \mid D_o(t), D_n(t), T(t)\}$$
$$= \phi D_n(t)\Delta + o(\Delta)$$

$$P\{(D_o(t+\Delta), D_n(t+\Delta), T(t+\Delta)) = (D_o(t)-1, D_n(t), T(t)) \mid D_o(t), D_n(t), T(t)\}$$
$$= \lambda_o(T(t)) D_o(t)\Delta + o(\Delta)$$

$$P\{(D_o(t+\Delta), D_n(t+\Delta), T(t+\Delta)) = (D_o(t), D_n(t)+1, T(t)) \mid D_o(t), D_n(t), T(t)\}$$
$$= \mu(T(t))(C - D_n(t) - D_o(t))\Delta + o(\Delta)$$

$$P\{(D_o(t+\Delta), D_n(t+\Delta), T(t+\Delta)) = (D_o(t), D_n(t)-1, T(t)) \mid D_o(t), D_n(t), T(t)\}$$
$$= \lambda_n(T(t)) D_n(t)\Delta + o(\Delta)$$

$$P\{(D_o(t+\Delta), D_n(t+\Delta), T(t+\Delta)) = (D_o(t), D_n(t), T(t)+1) \mid D_o(t), D_n(t), T(t)\}$$
$$= \tau(t)\Delta + o(\Delta)$$

$$P\{(D_o(t+\Delta), D_n(t+\Delta), T(t+\Delta)) = (D_o(t), D_n(t), T(t)-1) \mid D_o(t), D_n(t), T(t)\}$$
$$= \left[\frac{\upsilon_n T(t)}{1+\kappa_n T(t)} D_n(t) + \frac{\upsilon_o T(t)}{1+\kappa_o T(t)} D_o(t)\right]\Delta + o(\Delta)$$

$$P\{(D_o(t+\Delta), D_n(t+\Delta), T(t+\Delta)) = (D_o(t), D_n(t), T(t)) \mid D_o(t), D_n(t), T(t)\}$$
$$= 1 - p(D_o(t), D_n(t), T(t))\Delta + o(\Delta)$$

where

$$p(D_o(t), D_n(t), T(t)) = \phi D_n(t) + \lambda_o(T(t))D_o(t) + \mu(T(t))(C - D_n(t) - D_o(t))$$
$$+\lambda_n(T(t))D_n(t) + \tau(t)$$
$$+\frac{\upsilon_n T(t)}{1+\kappa_n T(t)} D_n(t) + \frac{\upsilon_o T(t)}{1+\kappa_o T(t)} D_o(t)$$

Asymptotics for C Large.

In this subsection we invoke the techniques applied for the Markovian model of Cell-Toxin interaction to obtain a limiting trivariate normal distribution for the number of young and old cell pairs and amount of toxin in the organ as the number of cells in the organ $C \to \infty$.

Define the joint moment generating function, (assumed to exist), to be

$$\psi(\theta_o, \theta_n, \theta_t; t) \overset{(d)}{=} E\left[\exp\left\{\theta_o D_o(t) + \theta_n D_n(t) + \theta_t T(t)\right\}\right]. \tag{5.32}$$

Use the Markov property to derive the forward equations in transform space:

$$\begin{aligned}
&E\left[\exp\left\{\theta_o D_o(t+\Delta) + \theta_n D_n(t+\Delta) + \theta_t T(t+\Delta)\right\} \middle| D_o(t), D_n(t), T(t)\right] \\
&= \exp\left\{\theta_o(D_o(t)+1) + \theta_n(D_n(t)-1) + \theta_t T(t)\right\}\phi D_n(t)\Delta \\
&+ \exp\left\{\theta_o(D_o(t)-1) + \theta_n D_n(t) + \theta_t T(t)\right\}\lambda_o(T(t))D_o(t)\Delta \\
&+ \exp\left\{\theta_o D_o(t) + \theta_n(D_n(t)+1) + \theta_t T(t)\right\}\mu(T(t))(C - D_n(t) - D_o(t))\Delta \\
&+ \exp\left\{\theta_o D_o(t) + \theta_n(D_n(t)-1) + \theta_t T(t)\right\}\lambda_n(T(t))D_n(t)\Delta \\
&+ \exp\left\{\theta_o D_o(t) + \theta_n D_n(t) + \theta_t(T(t)+1)\right\}\tau(t)\Delta \\
&+ \exp\left\{\theta_o D_o(t) + \theta_n D_n(t) + \theta_t(T(t)-1)\right\}\left[\frac{\upsilon_n T(t) D_n(t)}{1+\kappa_n T(t)} + \frac{\upsilon_o T(t) D_o(t)}{1+\kappa_o T(t)}\right]\Delta \\
&+ \exp\left\{\theta_o D_o(t) + \theta_n D_n(t) + \theta_t(T(t))\right\}\left[1 - p(D_o(t), D_n(t), T(t))\Delta\right] + o(\Delta).
\end{aligned} \tag{5.33}$$

After rearrangement and division by Δ, letting $\Delta \to 0$, and putting $Z(t) = \exp\{\theta_o D_o(t) + \theta_n D_n(t) + \theta_t T(t)\}$

$$\begin{aligned}
&\frac{d\Psi(\theta_o,\theta_n,\theta_t)}{dt} \\
&= \left(e^{\theta_o-\theta_n}-1\right)E\left[Z(t)\phi D_n(t)\right] \\
&+\left(e^{-\theta_o}-1\right)E\left[Z(t)\lambda_o(T(t))D_o(t)\right] \\
&+\left(e^{\theta_n}-1\right)E\left[Z(t)\mu(T(t))(C-D_o(t)-D_n(t))\right] \\
&+\left(e^{-\theta_n}-1\right)E\left[Z(t)\lambda_n(T(t))D_n(t)\right] \\
&+\left(e^{\theta_t}-1\right)\tau(t)E\left[Z(t)\right] \\
&+\left(e^{-\theta_t}-1\right)E\left[Z(t)\left[\frac{\upsilon_n T(t)D_n(t)}{1+\kappa_n T(t)}+\frac{\upsilon_o T(t)D_o(t)}{1+\kappa_o T(t)}\right]\right].
\end{aligned} \tag{5.34}$$

Define as before

$$X_o(t)=\frac{D_o(t)-C\alpha_o(t)}{\sqrt{C}},\ X_n(t)=\frac{D_n(t)-C\alpha_n(t)}{\sqrt{C}},\ Y(t)=\frac{T(t)-C\beta(t)}{\sqrt{C}} \tag{5.35}$$

and the joint mgf of the scaled "noise" variables $X_o(t)$, $X_n(t)$, $Y(t)$:

$$\begin{aligned}
\varphi(\theta_o,\theta_n,\theta_t;t) &\overset{(d)}{=} E\left[\exp\left\{\theta_o X_o(t)+\theta_n X_n(t)+\theta_t Y(t)\right\}\right] \\
&= \Psi\left(\frac{\theta_o}{\sqrt{C}},\frac{\theta_n}{\sqrt{C}},\frac{\theta_t}{\sqrt{C}}\right)\exp\left\{-\sqrt{C}\left(\theta_o\alpha_o(t)+\theta_n\alpha_n(t)+\theta_t\beta(t)\right)\right\}.
\end{aligned} \tag{5.36}$$

Proceeding as in the derivation of (5.11)

$$\frac{d\varphi}{dt}\exp\left\{\sqrt{C}\left(\theta_o\alpha_o(t)+\theta_n\alpha_n(t)+\theta_t\beta(t)\right)\right\}$$

$$+\varphi\sqrt{C}\left(\theta_o\alpha_o'(t)+\theta_n\alpha_n'(t)+\theta_t\beta'(t)\right)\exp\left\{\sqrt{C}\left(\theta_o\alpha_o(t)+\theta_n\alpha_n(t)+\theta_t\beta(t)\right)\right\}$$

$$=E\Bigg[\exp\left\{\left(\theta_o/\sqrt{C}\right)\left(\sqrt{C}X_o(t)+C\alpha_o(t)\right)+\left(\theta_n/\sqrt{C}\right)\left(\sqrt{C}X_n(t)+C\alpha_n(t)\right)\right.$$

$$\left.+\left(\theta_t/\sqrt{C}\right)\left(\sqrt{C}Y(t)+C\beta(t)\right)\right\}$$

$$\times\Bigg\{\left(e^{(\theta_o-\theta_n)/\sqrt{C}}-1\right)\phi\left(C\alpha_n+\sqrt{C}X_n(t)\right)$$

$$+\left(e^{-\theta_o/\sqrt{C}}-1\right)\lambda_o\left(C\beta(t)+\sqrt{C}Y(t)\right)\left(C\alpha_o(t)+\sqrt{C}X_o(t)\right)$$

$$+\left(e^{\theta_n/\sqrt{C}}-1\right)\mu\left(C\beta(t)+\sqrt{C}Y(t)\right)\left(C(1-\alpha_o(t)-\alpha_n(t))-\sqrt{C}X_o(t)-\sqrt{C}X_n(t)\right)$$

$$+\left(e^{-\theta_n/\sqrt{C}}-1\right)\lambda_n\left(C\beta(t)+\sqrt{C}Y(t)\right)\left(C\alpha_n(t)+\sqrt{C}X_n(t)\right)$$

$$+\left(e^{\theta_t/\sqrt{C}}-1\right)\tau(t)$$

$$+\left(e^{-\theta_t/\sqrt{C}}-1\right)\left[\frac{\upsilon_n\left(C\beta(t)+\sqrt{C}Y(t)\right)\left(C\alpha_n(t)+\sqrt{C}X_n(t)\right)}{1+\kappa_n\left(C\beta(t)+\sqrt{C}Y(t)\right)}\right] \tag{5.37}$$

$$\left.+\left(e^{-\theta_t/\sqrt{C}}-1\right)\left[\frac{\upsilon_o\left(C\beta(t)+\sqrt{C}Y(t)\right)\left(C\alpha_o(t)+\sqrt{C}X_o(t)\right)}{1+\kappa_o\left(C\beta(t)+\sqrt{C}Y(t)\right)}\right]\right\}\Bigg].$$

Next scale the transition rates as before

$$\mu\left(C\beta(t)+\sqrt{C}Y(t)\right)=\mu_0^*(\beta(t))+\mu_1^*(\beta(t))\frac{Y(t)}{\sqrt{C}} \tag{5.38a}$$

$$\lambda_o\left(C\beta(t)+\sqrt{C}Y(t)\right)=\lambda_{o,0}^*(\beta(t))+\lambda_{o,1}^*(\beta(t))\frac{Y(t)}{\sqrt{C}} \tag{5.38b}$$

$$\lambda_n\left(C\beta(t)+\sqrt{C}Y(t)\right)=\lambda_{n,0}^*(\beta(t))+\lambda_{n,1}^*(\beta(t))\frac{Y(t)}{\sqrt{C}} \tag{5.38c}$$

$$\upsilon=\upsilon^*/C \qquad \tau(t)=C\tau^*(t) \tag{5.38d}$$

$$\kappa_o^*=C\kappa_o \qquad \kappa_n^*=C\kappa_n \tag{5.38e}$$

Substituting into equation (5.37) and identifying terms results in the following equations.

The terms of order $\sqrt{C}$ imply that $\alpha_o(t)$, $\alpha_n(t)$, and $\beta(t)$ satisfy the differential equations

$$\alpha_o'(t)=\phi\alpha_n(t)-\lambda_{o0}^*(\beta(t))\alpha_o(t) \tag{5.39a}$$

$$\alpha_n'(t)=\mu_0^*(\beta(t))(1-\alpha_o(t)-\alpha_n(t))-\phi\alpha_n(t)-\lambda_{n0}^*(\beta(t))\alpha_n(t) \tag{5.39b}$$

$$\beta'(t)=\tau^*(t)-\frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t)-\frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t). \tag{5.39c}$$

These equations are scaled versions of equations (3.16) – (3.18).

The terms of order $\left(\sqrt{C}\right)^0$ result in the following equations.

$$\frac{\partial \varphi_0}{\partial t} = \left(\frac{\theta_o^2}{2} A_o(t) + \frac{\theta_n^2}{2} A_n(t) + \frac{\theta_t^2}{2} A_t(t) - \theta_o \theta_n \phi \alpha_n \right) \varphi_o$$
$$+ \theta_o \left[B_{o,o} \frac{\partial \varphi_0}{\partial \theta_o} + B_{o,n} \frac{\partial \varphi_0}{\partial \theta_n} + B_{o,t} \frac{\partial \varphi_0}{\partial \theta_t} \right]$$
$$+ \theta_n \left[B_{n,o} \frac{\partial \varphi_0}{\partial \theta_o} + B_{n,n} \frac{\partial \varphi_0}{\partial \theta_n} + B_{n,t} \frac{\partial \varphi_0}{\partial \theta_t} \right]$$
$$+ \theta_t \left[\beta_{t,o} \frac{\partial \varphi_0}{\partial \theta_o} + B_{t,n} \frac{\partial \varphi_0}{\partial \theta_n} + B_{t,t} \frac{\partial \varphi_0}{\partial \theta_t} \right] \tag{5.40}$$

where

$$A_o(t) = \phi \alpha_n(t) + \lambda^*_{o,0}(\beta(t)) \alpha_o(t) \tag{5.41a}$$

$$A_n(t) = \mu^*_0(\beta(t))[1 - \alpha_o(t) - \alpha_n(t)] + \lambda_{n,0}(\beta(t)) \alpha_n(t) + \phi \alpha_n(t) \tag{5.41b}$$

$$A_t(t) = \frac{\upsilon^*_n}{1 + \kappa^*_n \beta(t)} \beta(t) \alpha_n(t) + \frac{\upsilon^*_o}{1 + \kappa^*_o \beta(t)} \beta(t) \alpha_o(t) + \tau^* \tag{5.41c}$$

$$B_{o,o} = -\lambda^*_{o,0}(\beta(t)) \tag{5.41d}$$

$$B_{o,n} = \phi \tag{5.41e}$$

$$B_{o,t} = -\lambda^*_{o,1}(\beta(t)) \alpha_o(t) \tag{5.41f}$$

$$B_{n,o} = -\mu^*_0(\beta(t)) \tag{5.41g}$$

$$B_{n,n} = -\mu^*_0(\beta(t)) - \lambda^*_{n,0}(\beta(t)) - \phi \tag{5.41h}$$

$$B_{n,t} = \mu^*_1(\beta(t))(1 - \alpha_o(t) - \alpha_n(t)) - \alpha_n(t) \lambda^*_{n,1}(\beta(t)) \tag{5.41i}$$

$$B_{t,o} = \frac{-\upsilon^*_o \beta(t)}{1 + \kappa^*_o \beta(t)} \quad B_{t,n} = \frac{-\upsilon^*_n \beta(t)}{1 + \kappa^*_n \beta(t)} \tag{5.41j}$$

$$B_{t,t} = \frac{-\upsilon_n \alpha_n(t)}{1 + \kappa^*_n \beta(t)} \left[1 - \frac{\kappa^*_n \beta(t)}{1 + \kappa^*_n \beta(t)} \right] - \frac{\upsilon_o \alpha_o(t)}{1 + \kappa^*_o \beta(t)} \left[1 - \frac{\kappa^*_o \beta(t)}{1 + \kappa^*_o \beta(t)} \right]. \tag{5.41k}$$

Finally, calculations similar to those leading to (5.23) – (5.27) result in

$$\frac{d}{dt}E\left[X_o^2(t)\right] = A_o \quad +2B_{o,o}E\left[X_o^2(t)\right] +2B_{o,n}E\left[X_o(t)X_n(t)\right] +2B_{o,t}E\left[X_o(t)T(t)\right] \tag{5.42a}$$

$$\frac{d}{dt}E\left[X_n^2(t)\right] = A_n \quad +2B_{n,o}E\left[X_o(t)X_n(t)\right] +2B_{n,n}E\left[X_n^2(t)\right] +2B_{n,t}E\left[X_n(t)T(t)\right] \tag{5.42b}$$

$$\frac{d}{dt}E\left[T^2(t)\right] = A_t \quad +2B_{t,o}E\left[X_o(t)T(t)\right] +2B_{t,n}E\left[X_n(t)T(t)\right] +2B_{t,t}E\left[T^2(t)\right] \tag{5.42c}$$

$$\frac{d}{dt}E\left[X_o(t)T(t)\right] = \left[B_{o,o} + B_{t,t}\right]E\left[X_o(t)T(t)\right] +B_{o,n}E\left[X_n(t)T(t)\right] + B_{t,n}E\left[X_o(t)X_n(t)\right] + B_{o,t}E\left[T^2(t)\right] +B_{t,o}E\left[X_o^2(t)\right] \tag{5.42d}$$

$$\frac{d}{dt}E\left[X_n(t)T(t)\right] = B_{n,o}E\left[X_o(t)T(t)\right] + \left(B_{n,n} + B_{t,t}\right)E\left[X_n(t)T(t)\right] +B_{t,o}E\left[X_o(t)X_n(t)\right] + B_{t,n}E\left[X_n^2(t)\right] + B_{n,t}E\left[T^2(t)\right] \tag{5.42e}$$

$$\frac{d}{dt}E[X_o(t)X_n(t)] = (B_{o,o} + B_{n,n})E[X_o(t)X_n(t)]$$
$$+B_{n,t}E[X_o(t)T(t)]$$
$$+B_{o,t}E[X_n(t)T(t)]$$
$$+B_{n,o}E[X_o^2(t)]$$
$$+B_{o,n}E[X_n^2(t)]$$
$$-\phi\alpha_n \qquad (5.42f)$$

The parameters in equations (5.19), (5.25) – (5.27) are as follows:

For the case $\mu(T) = \mu e^{-\xi T}$,

$$\mu^*(\beta(t) + Y(t)/\sqrt{C}) = \mu \exp\{-\xi^*(\beta(t) + Y(t)/\sqrt{C})\}$$
$$= \mu^*(\beta(t)) + \mu_1^*(\beta(t))\frac{Y(t)}{\sqrt{C}}$$

where

$$\xi^* = \xi C$$
$$\mu_0^*(\beta(t)) = \mu e^{-\xi^*\beta(t)}$$
$$\mu_1^*(\beta(t)) = -\mu\xi^* e^{-\xi^*\beta(t)}.$$

Similarly, if $\lambda_o(T) = \lambda_0 e^{\eta_o T}$, then

$$\lambda_o^*(\beta(t) + Y(t)/\sqrt{C}) = \lambda_o \exp\{\eta_o^*(\beta(t) + Y(t)/\sqrt{C})\}$$
$$= \lambda_{o,0}^*(\beta(t)) + \lambda_{o,1}^*(\beta(t))\frac{Y(t)}{\sqrt{C}}$$

where

$$\eta_o^* = \eta_o C$$
$$\lambda_{o,0}^*(\beta(t)) = \lambda_o e^{\eta_o^*\beta(t)}$$
$$\lambda_{o,1}^*(\beta(t)) = \lambda_o \eta_o^* e^{\eta_o^*\beta(t)}.$$

Also

$$\lambda_n^*\left(\beta(t)+Y(t)/\sqrt{C}\right)=\lambda_n\left[\exp\left\{\eta_n^*\left(\beta(t)+Y(t)/\sqrt{C}\right)\right\}-1\right]$$

$$=\lambda_{n,0}^*(\beta(t))+\lambda_{n,1}(\beta(t))\frac{Y(t)}{\sqrt{C}}$$

where

$$\eta_n^*=\eta_n C$$

$$\lambda_{n,0}^*(\beta(t))=\lambda_n\left[e^{\eta_n^*\beta(t)}-1\right]$$

$$\lambda_{n,1}^*(\beta(t))=\lambda_n\eta_n^* e^{\eta_n^*\beta(t)}.$$

$$\kappa_o^*=\kappa_o C$$

$$\kappa_n^*=\kappa_n C$$

$$\tau^*(t)=\tau(t)/C$$

$$\upsilon^*=\upsilon C.$$

A steady-state solution to equations (5.39a) – (5.39c) for a constant toxin input $\tau(t)\equiv\tau$ would satisfy

$$0=\phi\alpha_n-\lambda_o e^{\eta_o^*\beta}\alpha_o \tag{5.43a}$$

$$0=\mu e^{-\xi^*\beta}(1-\alpha_o-\alpha_n)-\phi\alpha_n-\lambda_n\left(e^{\eta_n^*\beta}-1\right)\alpha_n \tag{5.43b}$$

$$0=\tau^*-\frac{1}{1+\kappa_n^*\beta}\upsilon_n^*\beta\alpha_n-\frac{1}{1+\kappa_o^*\beta}\upsilon_o^*\beta\alpha_o \tag{5.43c}$$

where we are using functions of the form

$$\lambda_o(T)=\lambda_o e^{\eta_o T}$$

$$\lambda_n(T)=\lambda_n\left(e^{\eta_n T}-1\right)$$

$$\mu(T)=\mu e^{-\xi T}$$

with

$$\eta_o^* = \eta_o C, \xi^* = \xi C, \eta_n^* = \eta_n C, \upsilon_n^* = \upsilon_n C, \upsilon_o^* = \upsilon_o C, \kappa_n^* = \kappa_n C, \kappa_o^* = \kappa_o C, \tau^* = \tau / C.$$

Simplification of (5.43a) and (5.43b) results in

$$\alpha_o = \frac{\phi}{\lambda_o} e^{-\eta_o^* \beta} \alpha_n \tag{5.44a}$$

$$\alpha_n = \mu e^{-\xi^* \beta} \left[\lambda_n \left(e^{\eta_n^* \beta} - 1 \right) + \phi + \mu e^{-\xi^* \beta} \left(1 + \frac{\phi}{\lambda_o} e^{-\eta_o^* \beta} \right) \right]^{-1} \tag{5.44b}$$

Finally expression (5.44a) and (5.44b) can be substituted into equation (5.43c) to obtain an equation for β. This latter equation can have 0, 1, or 2 solutions. If it has no solution, then $\alpha_n = \alpha_o = 0$ and the organ is dead. If the equation has two solutions, then the smaller of the two possible solutions is biologically plausible since the smaller solution is an increasing function of τ, whereas the larger solution is a decreasing function.

Numerical Examples

The following parameter values are used in the numerical examples below. $\upsilon_o = 0.05$, $\mu = 0.5$, $\eta_o = 1$, $\xi = 0.5$, $\kappa_o = 1$, $\lambda_o = 0.08$, $\upsilon_n = 0.1$, $\eta_n = 0.5$, $\kappa_n = 1$, $\lambda_n = 0.05$, $\phi = 0.1$, $C = 10^7$.

Figures 6 – 9 present results for the case in which $\tau(t) = 0$ for $0 \le t \le 2$ and then $\tau(t) = 4 \times 10^5$ for $t > 2$. The moments are started at their steady state values for no toxin input. Figure 6 presents the mean number of old cell pairs, $C \times \alpha_o(t)$, and the standard deviation of the number of old cell pairs, $\left[C \times E\left[X_o^2(t) \right] \right]^{1/2}$. Note that the mean number of old cell pairs decreases to a new steady state value below the value for no toxin; the standard deviation increases, then decreases, then increases again to a new steady state value which is higher than the value for no toxin. Figure 7 presents the mean number of young/new cell pairs, $C \times \alpha_n(t)$, and

the standard deviation of young/new cell pairs $\left[C \times E\left[X_n^2(t)\right]\right]^{1/2}$. The mean number increases to a steady state value larger than that for no toxin input; the standard deviation initially decreases, then increases and finally decreases to a new steady state value below the value for no toxin. Figure 8 presents the mean number of totally differentiated cell pairs, $C \times (\alpha_0(t) + \alpha_n(t))$, and the standard deviation of the number of totally differentiated cell pairs

$$\left[C \times \left[E\left[X_0^2(t)\right] + 2E\left[X_0(t)X_n(t)\right] + E\left[X_n^2(t)\right]\right]\right]^{1/2}.$$

The mean number decreases to a new steady state value below the value for no toxin; the standard deviation increases to a new steady state value. Figure 9 presents the mean amount of toxin, $C \times \beta(t)$, and the standard deviation $\left[C \times E\left[T^2(t)\right]\right]^{1/2}$. Both values increase to a steady state value.

Figures 10 – 13 present results for a large input of toxin for a short time period: approximately a *bolus* input. The input of toxin is $\tau(t) = 40 \times 10^5$ for $2 < t \leq 3$ and $\tau(t) = 0$ otherwise. Figure 10 presents the mean number of totally differentiated cell pairs and the standard deviation of totally differentiated cell pairs. The mean number initially decreases, then increases to the steady state value with no toxin. The standard deviation initially increases, then decreases to the steady state value with no toxin. Figure 11 displays the mean number of old cell pairs and the standard deviation of old cell pairs. The mean number initially decreases, then returns to the steady state value with no toxin. The standard deviation initially decreases, then increases, then returns to the steady state value with no toxin. Figure 12 displays the mean and standard deviation of the number of young/new cell pairs. The mean number initially decreases, then increases, after which it returns to the steady state value with no toxin. The standard

deviation exhibits similar behavior but on a different scale. Figure 13 presents the mean and standard deviation of the amount of toxin.

Figures 14 – 17 present results for the same parameter values and same toxin input as Figures 10 – 13 except that $\phi = 0.01$ instead of 0.1; that is, the mean time until a young/new cell pair becomes an old cell pair is 100 = 1/0.01 rather than 10 = 1/0.1. This should increase the number of young/new cell pairs. Figure 16 shows that the mean number of young/new cells is indeed larger. Figure 14 presents the mean and standard deviation of the number of totally differentiated cell pairs. Note that the mean initially decreases, then increases to *overshoot* the steady state value with no toxin. The mean then decreases to the steady state value with no toxin. This behavior of overshooting the steady state value with no toxin has been observed in experimental studies; Portier (1993).

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APPENDIX A

Isham-Whittle Theory

In this Appendix we present another approach to approximating the non-linear expectations in equations (5.3) and (5.4). We follow the example of Isham (1991) and Whittle (1957) by (a) writing equations for second moments and joint transforms, and (b) "closing" the system of lower-moment equations by assuming that $(D(t), T(t))$ is bivariate Gaussian; we call this approach *Gaussian closure* (GC). The plausibility of this assumption follows from Model D.1 above. Asymptotic perturbation methods in section 5 will show that a bivariate Gaussian process is of natural occurrence if the system of cells is large, as is true in practice.

To proceed, we write second-moment equations:

$$E\left[D^2(t+\Delta)|D(t),T(t)\right] = \left(D(t)+1\right)^2 \mu\left(T(t)\right)\left(C-D(t)\right)\Delta + \left(D(t)-1\right)^2 \lambda\left(T(t)\right)D(t)\Delta$$
$$+D^2(t)\left[1-\left(\mu\left(T(t)\right)\left(C-D(t)\right)\Delta - \lambda\left(T(t)\right)D(t)\Delta\right)\right] + o(\Delta).$$

Simplification and limit-taking provides

$$\boxed{\begin{aligned}\frac{d}{dt}E\left[D^2(t)\right] &= 2E\left[D(t)\mu\left(T(t)\right)\left(C-D(t)\right)\right] - 2E\left[D^2(t)\lambda\left(T(t)\right)\right] \\ &\quad +E\left[\mu\left(T(t)\right)\left(C-D(t)\right)\right] + E\left[\lambda\left(T(t)\right)D(t)\right]\end{aligned}} \tag{A.1}$$

$$E\left[T^2(t+\Delta)|D(t),T(t)\right] = \left(T(t)+1\right)^2 \tau(t)\Delta$$
$$+\left(T(t)-1\right)^2 \upsilon\frac{D(t)T(t)}{1+\kappa T(t)} + T^2(t)\left[1-\left(\tau(t)\Delta + \upsilon\frac{D(t)T(t)}{1+\kappa T(t)}\Delta\right)\right] + o(\Delta)$$

from which

$$\boxed{\frac{d}{dt}E\left[T^2(t)\right] = 2\tau(t)E\left[T(t)\right] + \tau(t) - 2\upsilon E\left[\frac{D(t)T^2(t)}{1+\kappa T(t)}\right] + \upsilon E\left[\frac{D(t)T(t)}{1+\kappa T(t)}\right]} \quad \text{(A.2)}$$

Next

$$E\left[D(t+\Delta)T(t+\Delta)\middle|D(t),T(t)\right] = \left(D(t)+1\right)\left(T(t)\right)\mu\left(T(t)\right)\left(C-D(t)\right)\Delta$$

$$+\left(D(t)-1\right)\left(T(t)\right)\lambda\left(T(t)\right)D(t)\Delta + D(t)\left(T(t)+1\right)\tau(t)\Delta + D(t)\left(T(t)-1\right)\upsilon\frac{D(t)T(t)}{1+\kappa T(t)}\Delta$$

$$+D(t)T(t)\left[1-\mu\left(T(t)\right)\left(C-D(t)\right)\Delta + \lambda\left(T(t)\right)D(t)\Delta + \tau(t)\Delta + \upsilon\frac{D(t)T(t)}{1+\kappa T(t)}\Delta\right]$$

which leads to

$$\boxed{\begin{aligned}\frac{d}{dt}E\left[D(t)T(t)\right] &= E\left[T(t)\mu\left(T(t)\right)\left(C-D(t)\right)\right] - E\left[T(t)\lambda\left(T(t)\right)D(t)\right] \\ &\quad + \tau(t)E\left[D(t)\right] - \upsilon E\left[D(t)\cdot\frac{D(t)T(t)}{1+\kappa T(t)}\right].\end{aligned}} \quad \text{(A.3)}$$

In order to go further, it is necessary to parameterize the rate parameters and the Michaelis-Menten (M.-M.) term. We set as before, for $\xi, \mu > 0$,

$$\mu(T) = \mu_0 e^{-\xi T},\ \lambda(T) = \lambda_0 e^{\eta T}. \quad \text{(A.4)}$$

If $(D(t),\ T(t))$ has a bivariate normal distribution, then the distribution is determined by the marginal means, the marginal variances and the covariance. Other moments can be expressed in terms of these qualities. For example

$$E\left[D^2(t)T(t)\right] = E[D(t)]^2 E[T(t)]$$
$$+2E[D(t)]Cov[D(t),T(t)]$$
$$+E[T(t)]Var[D(t)] \qquad \text{(A.5)}$$

Equations (5.3) – (5.4), (A.1) – (A.3) can be evaluated using the following approximate numerical procedure. Put
$m_D(t) = E[D(t)]$, $m_T(t) = E[T(t)]$, $m_{D^2}(t) = E\left[D^2(t)\right]$ $m_{T^2}(t) = E\left[T^2(t)\right]$, and
$m_{DT}(t) = E[D(t)T(t)]$.

$$m_D(t+\Delta) = m_D(t) + \Delta\left\{\mu(m_T(t))C - \left(\mu(m_T(t)) + \lambda(m_T(t))\right)m_D(t)\right\} \qquad \text{(5.3a)}$$

$$m_T(t+D) = m_T(t) + \Delta\left\{\tau(t) - \upsilon\frac{1}{1+\kappa m_T(t)}m_{DT}(t)\right\} \qquad \text{(5.4a)}$$

$$m_{D^2}(t+\Delta) = m_{D^2}(t)$$
$$+\Delta\left\{2\mu(m_T(t))C_{mD}(t) - 2\left(\mu(m_T(t)) + \lambda(m_T(t))\right)m_{D^2}(t)\right.$$
$$\left.+\mu(m_T(t))C + \left(\lambda(m_T(t)) - \mu(m_T(t))\right)m_D(t)\right\} \qquad \text{(A.1a)}$$

$$m_{T^2}(t+\Delta) = m_{T^2}(t)$$
$$+\Delta\left\{2\tau(t)m_T(t) + \tau(t) - 2\upsilon\frac{1}{1+\kappa m_T(t)}E\left[D(t)T^2(t)\right]\right.$$
$$\left.+\frac{\upsilon}{1+\kappa m_T(t)}m_{DT}(t)\right\} \qquad \text{(A.2a)}$$

$$m_{DT}(t+\Delta) = m_{DT}(t)$$
$$+\Delta\left\{\mu(m_T(t))Cm_T(t) - \left(\lambda(m_T(t)) + \mu(m_T(t))\right)m_{DT}(t)\right.$$
$$\left.+\tau(t)m_D(t) - \upsilon\frac{1}{1+\kappa m_T(t)}E\left[D^2(t)T(t)\right]\right\} \qquad \text{(A.3a)}$$

The higher order moments $E[D(t)T^2(t)]$ and $E[D^2(t)T(t)]$ are evaluated using the expressions for a bivariate normal distribution such as (A.5).

Comparison of the Two Systems of Moment Equations.

In this section we study the limit as $C \to \infty$ of Equations (5.3) – (5.4) and (A.1) – (A.3) using the scaling of the transition rates (5.12a) – (5.12d). The limits of the equations are as follows.

$$\frac{d}{dt}\alpha(t) = \mu_0^*(\beta(t))(1-\alpha(t)) - \lambda_0^*(\beta(t))\alpha(t) \tag{5.3b}$$

$$\frac{d}{dt}\beta(t) = \tau^* - \upsilon^* \frac{\alpha(t)\beta(t)}{1+\kappa^*\beta(t)} \tag{5.4b}$$

$$\begin{aligned}\frac{d}{dt}E\left[X^2(t)\right] &= A_d(t) + E\left[X^2(t)\right]2B_{dd} \\ &\quad +2B_{td}E[X(t)Y(t)] \\ &\quad -2\alpha(t)\left[\mu_1^*(\beta(t)) + \lambda_1^*(\beta(t))\right]E[X(t)Y(t)]\end{aligned} \tag{A.1b}$$

$$\begin{aligned}\frac{d}{dt}E\left[Y^2(t)\right] &= A_t(t) + 2B_{tt}E\left[Y^2(t)\right] \\ &\quad +2B_{dt}E[X(t)Y(t)] \\ &\quad +2\frac{\upsilon^*\kappa^*\alpha(t)\beta(t)}{\left(1+\kappa^*\beta(t)\right)^2}E\left[Y^2(t)\right] \\ &\quad -2\frac{\upsilon^*\beta(t)}{1+\kappa^*\beta(t)}\left[1-\frac{\beta(t)\kappa^*}{1+\kappa^*\beta(t)}\right]E[X(t)Y(t)]\end{aligned} \tag{A.2b}$$

$$\frac{d}{dt}E[X(t)Y(t)] = (B_{dd} + B_{tt})E[X(t)Y(t)]$$
$$+B_{dt}E\left[X^2(t)\right] + B_{td}E\left[Y^2(t)\right]$$
$$+E\left[Y^2(t)\right]\frac{\upsilon^*\kappa^*\alpha(t)^2}{(1+\kappa\beta(t))^2}$$
$$+E[X(t)Y(t)]\left\{B_{tt} - \beta\left[\mu_1^* + \lambda_1^*\right]\right\} \qquad \text{(A.3a)}$$

The fact that the second moment equations (A.1a) – (A.3a) contain more terms than (5.25) – (5.27) is due to the difference between a) first taking the limit as $C \to \infty$ for the joint distribution of $(D(t), T(t))$ and then finding the second order moments of the limiting bivariate normal distribution and b) writing the differential equations for the second moments and then taking the limit as $C \to \infty$. In the latter case, it appears that the effects of higher order moments become important.

An example calculation follows. Rewriting equation (A.3) using (5.8)

$$\frac{d}{dt}E\left[\left(C\alpha(t)+C^{1/2}X(t)\right)\left(C\beta(t)+C^{1/2}Y(t)\right)\right]$$
$$= E\left[\mu\left(C\beta(t)+C^{1/2}Y(t)\right)\left[C\beta(t)+C^{1/2}Y(t)\right]\left[C(1-\alpha(t))-C^{1/2}X(t)\right]\right]$$
$$-E\left[\lambda\left(C\beta(t)+C^{1/2}Y(t)\right)\left[C\beta(t)+C^{1/2}Y(t)\right]\left[C\alpha(t)+C^{1/2}X(t)\right]\right]$$
$$+\tau(t)E\left[C\alpha(t)+C^{1/2}X(t)\right]$$
$$-\upsilon\frac{E\left[\left(C\alpha(t)+C^{1/2}X(t)\right)^2\left(C\beta(t)+C^{1/2}Y(t)\right)\right]}{1+\kappa\left(C\beta(t)+C^{1/2}Y(t)\right)} \qquad \text{(A.4)}$$

Next scale the transition rates using (5.12a) – (5.12d) and divide both sides of (A.4) by C. Equation (A.4) becomes

$$\frac{d}{dt}E\Big[C\alpha(t)\beta(t)+C^{1/2}\{\beta(t)X(t)+\alpha(t)Y(t)\}+X(t)Y(t)\Big]$$

$$=E\left[\left(\mu_0^*(\beta(t))+\mu_1^*(\beta(t))\frac{Y(t)}{\sqrt{C}}\right)\Big[C\beta(t)(1-\alpha(t))+C^{1/2}\big[(1-\alpha(t))Y(t)-\beta(t)X(t)\big]-X(t)Y(t)\Big]\right]$$

$$-E\left[\left(\lambda_0^*(\beta(t))+\lambda_1^*(\beta(t))\frac{Y(t)}{\sqrt{C}}\right)\Big[C\alpha(t)\beta(t)+C^{1/2}\big[\alpha(t)Y(t)+\beta(t)X(t)\big]+X(t)Y(t)\Big]\right]$$

$$+\tau^*(t)E\Big[C\alpha(t)+C^{1/2}X(t)\Big]$$

$$-\upsilon^*E\left[\left[\frac{1}{1+\kappa^*\beta(t)}-\frac{\kappa^*}{\left(1+\kappa^*\beta(t)\right)^2}\frac{Y(t)}{\sqrt{C}}\right]\Big[C\alpha(t)^2\beta(t)+2C^{1/2}\alpha(t)\beta(t)X(t)+X(t)^2\beta(t)\Big]\right]$$

$$-\upsilon^*E\left[\left[\frac{1}{1+\kappa^*\beta(t)}-\frac{\kappa^*}{\left(1+\kappa^*\beta(t)\right)^2}\frac{Y(t)}{\sqrt{C}}\right]\Big[\sqrt{C}\alpha(t)^2Y(t)+2\alpha(t)X(t)Y(t)+C^{-1/2}Y(t)X(t)^2\Big]\right] \tag{A.5}$$

If $\alpha(t)$ and $\beta(t)$ satisfy (5.19) then the equation corresponding to terms of order C in (A.5) is satisfied. The equation corresponding to terms of order $C^{1/2}$ in (A.2) is satisfied if

$$E[X(t)]=E[Y(t)]=\frac{d}{dt}E[X(t)]=\frac{d}{dt}E[Y(t)]=0.$$

The equation corresponding to terms of order C^0 in (A.5) is equation (A.3a). Equations corresponding to terms of other orders become 0 as $C\to\infty$.

APPENDIX B

Stochastic Fluid (Brownian Motion) Model of Toxic Level

The Markov chain model of (5.1) can be made more plausible and flexible by replacing the discrete state space by a continuous one. It is possible to allow $\{T(t)\}$, hereafter called toxicity, to move according to a Brownian motion or Wiener process with drift; both drift and diffusion coefficient can depend on the current number of differentiated cells and the toxicity.

Derivation of the replacement of the forward equation in transform form, (5.7), by the consequence of the above $T(t)$ representation gives (5.7) with the last two lines replaced by

$$\theta_t E\left[e^{\theta_d D(t)+\theta_t T(t)}\delta(D(t),T(t))\right]$$

$$+\frac{1}{2}\theta_t^2 E\left[e^{\theta_d D(t)+\theta_t T(t)}\sigma^2(D(t),T(t))\right]; \tag{B.1}$$

here $\delta(D(t), T(t))$ and $\sigma^2(D(t), T(t))$ are the Brownian/Wiener state-dependent drift and diffusion. In turn, these must be scaled:

$$\delta(D(t),T(t)) = C\delta^*\left(\alpha(t)+\frac{X(t)}{\sqrt{C}},\beta(t)+\frac{Y(t)}{\sqrt{C}}\right) \tag{B.2a}$$

$$\sigma^2(D(t),T(t)) = C\sigma^{2*}\left(\alpha(t)+\frac{X(t)}{\sqrt{C}},\beta(t)+\frac{Y(t)}{\sqrt{C}}\right) \tag{B.2b}$$

These functions can then be Taylor-series expanded to provide

$$\delta(D(t),T(t)) = C\delta^*(\alpha(t),\beta(t)) + \sqrt{C}\left(\delta_{11}^*(\alpha(t),\beta(t))X(t) + \delta_{12}^*(\alpha(t),\beta(t))Y(t)\right) + O(1) \tag{B.3a}$$

$$\sigma^2(D(t),T(t)) = C\sigma^{2*}(\alpha(t),\beta(t)) + \sqrt{C}\left(\sigma_{11}^{2*}(\alpha(t),\beta(t))X(t) + \sigma_{12}^{2*}(\alpha(t),\beta(t))Y(t)\right) + O(1) \tag{B.3b}$$

Now apply (5.9) and the new version of (5.11) after scaling as in (5.12); the change occurs in the last two lines of (5.11) as follows

$$\frac{\theta_t}{\sqrt{C}}E\left[e^{\theta_d X(t)+\theta_t Y(t)}\left(C\delta^*(\alpha(t),\beta(t))+\sqrt{C}\left(\delta_{11}^*(\alpha(t),\beta(t))X(t)+\delta_{12}^*(\alpha(t),\beta(t))Y(t)\right)\right)\right]$$

$$+\frac{1}{2}\frac{\theta_t^2}{C}E\left[e^{\theta_d X(t)+\theta_t Y(t)}\left(C\sigma^{2^*}(\alpha(t),\beta(t))+\sqrt{C}\left(\sigma_{11}^{2^*}(\alpha(t),\beta(t))X(t)\right.\right.\right.$$

$$\left.\left.\left.+\sigma_{12}^{2^*}(\alpha(t),\beta(t))X(t)+\sigma_{12}^{2^*}(\alpha(t),\beta(t))Y(t)\right)\right)\right]$$

$$=\sqrt{C}\theta_t\varphi\cdot\delta^*(\alpha(t),\beta(t))+\theta_t\left(\delta_{11}^*(\alpha(t),\beta(t))\frac{\partial\varphi}{\partial\theta_d}+\delta_{12}^*(\alpha(t),\beta(t))\frac{\partial\varphi}{\partial\theta_t}\right) \tag{B.4}$$

$$+\frac{1}{2}\theta_t^2\varphi\sigma^{2^*}(\alpha(t),\beta(t))+O\left(1/\sqrt{C}\right),$$

where δ_{11}^* and δ_{12}^* are partial derivatives of δ^* with respect to α and β, at $\alpha(t)$ and $\beta(t)$.

From (5.18) with the coefficient of θ_t changed as above, (B.4), we obtain the replacement for mean scaled toxicity,

$$\beta'(t)=\delta^*(\alpha(t),\beta(t))$$

and from (B.4) and (5.20) we now find

$$A_t(t)=\sigma^{2^*}(\alpha(t),\beta(t))$$

$$B_{dt}(t)=\delta_{11}^*(\alpha(t),\beta(t)),\quad B_{tt}(t)=\delta_{12}^*(\alpha(t),\beta(t)). \tag{B.5}$$

Example.

$$\delta(D(t),T(t))=\tau(t)-\frac{\upsilon(t)D(t)T(t)}{1+\kappa T(t)} \tag{B.6}$$

$$\sigma^2(D(t),T(t))=\sigma_i^2\tau(t)+\sigma_o^2\frac{\upsilon(t)D(t)T(t)}{1+\kappa T(t)}; \tag{B.7}$$

σ_i^2 and σ_o^2 are (here, but not necessarily) constants that permit adjustment of variances of toxic agent input $\left(\sigma_i^2\right)$ and output $\left(\sigma_o^2\right)$. Scaling as before,

$$\delta(D(t),T(t)) = C\tau^*(t) - \frac{\upsilon^*(t)}{C}\frac{\left(\left(C\alpha(t)+\sqrt{C}X(t)\right)\left(C\beta(t)+\sqrt{C}Y(t)\right)\right)}{1+\kappa^*\left(\beta(t)+Y(t)/\sqrt{C}\right)}$$

$$= C\left(\tau^*(t)-\upsilon^*(t)\right)\frac{\left(\left(\alpha(t)+X(t)/\sqrt{C}\right)\left(\beta(t)+Y(t)/\sqrt{C}\right)\right)}{1+\kappa^*\left(\beta(t)+Y(t)/\sqrt{C}\right)}$$

$$\equiv C\delta^*\left(\alpha(t)+X(t)/\sqrt{C},Y(t)/\sqrt{C}\right) \tag{B.8}$$

$$\sigma^2(D(t),T(t)) = C\left(\sigma_i^2\tau^*(t)+\sigma_0^2\frac{\upsilon^*(t)\left(\left(\alpha(t)+X(t)/\sqrt{C}\right)\left(\beta(t)+Y(t)/\sqrt{C}\right)\right)}{1+\kappa^*\left(\beta(t)+Y(t)/\sqrt{C}\right)}\right)$$

$$\equiv C\sigma^{2*}\left(\alpha(t)+X(t)/\sqrt{C},\beta(t)+Y(t)/\sqrt{C}\right) \tag{B.9}$$

From these we get

$$\frac{\partial\delta^*}{\partial\alpha} = -\upsilon^*(t)\frac{\beta(t)}{1+\kappa^*\beta(t)} \equiv \delta_{11}^*(\alpha(t),\beta(t)) = B_{dt}(t), \tag{B.10}$$

$$\frac{\partial\delta^*}{\partial\beta} = -\upsilon^*(t)\frac{\alpha(t)}{\left(1+\kappa^*\beta(t)\right)^2} \equiv \delta_{12}^*(\alpha(t),\beta(t)) = B_{tt}(t), \tag{B.11}$$

$$\sigma_i^2\tau^*(t)+\sigma_0^2\upsilon^*(t)\frac{\alpha(t)\beta(t)}{1+\kappa^*\beta(t)} \equiv \sigma^{2*}(\alpha(t),\beta(t)) = A_t(t). \tag{B.12}$$

Here $\kappa_0^*(\beta(t)) = \kappa^*\beta(t)$ and $\kappa_1^*(t) = \kappa^*$ in (5.21); the agreement with the previous model is apparent when $\sigma_i^2 = \sigma_0^2 = 1$. Note in particular that the model (5.1) represents toxic chemical input as a (time-dependent) Poisson process. To represent a deterministic inflow simply put $\sigma_i^2 = 0$, while to represent an extra-Poisson variability put $\sigma_i^2 > 1$. Variability in the output/removal of toxicity can be similarly modeled by adjusting σ_0^2.

Figures 1B, 2B, 3B present the standard deviation of the number of totally differentiated cell pairs for σ_i^2 =1, 5, and 20. Figure 1B has a constant input of

toxin. Figures 2B and 3B have a pulse of toxin but different values of ϕ. As σ_i^2 increases, the standard deviation of the number of totally differentiated cell pairs also increases.

F[TOX]

(NUN×TOX×DN÷(1+(KN×TOX)))+(NUO×TOX×DO÷(1+(KO×TOX)))

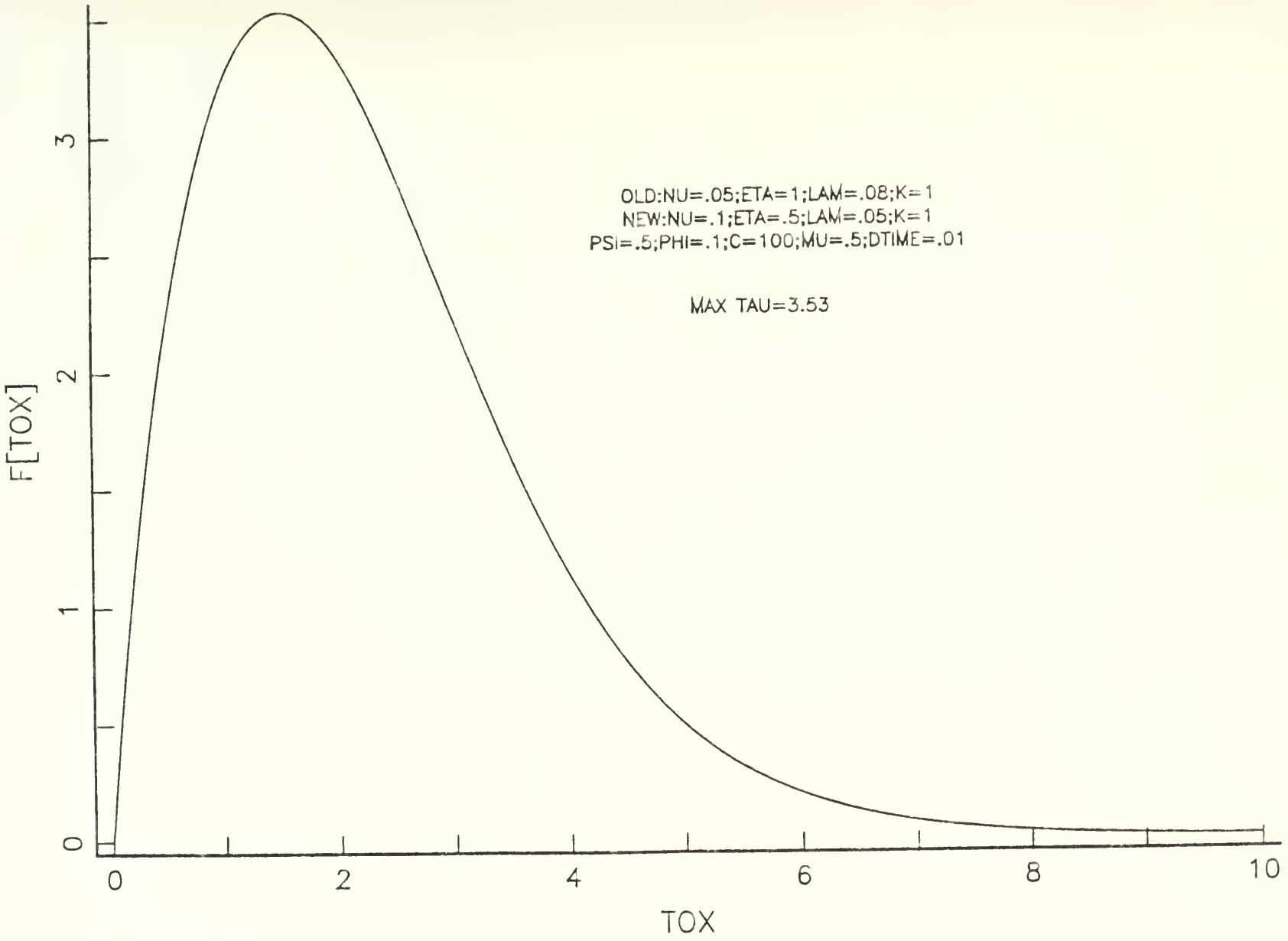
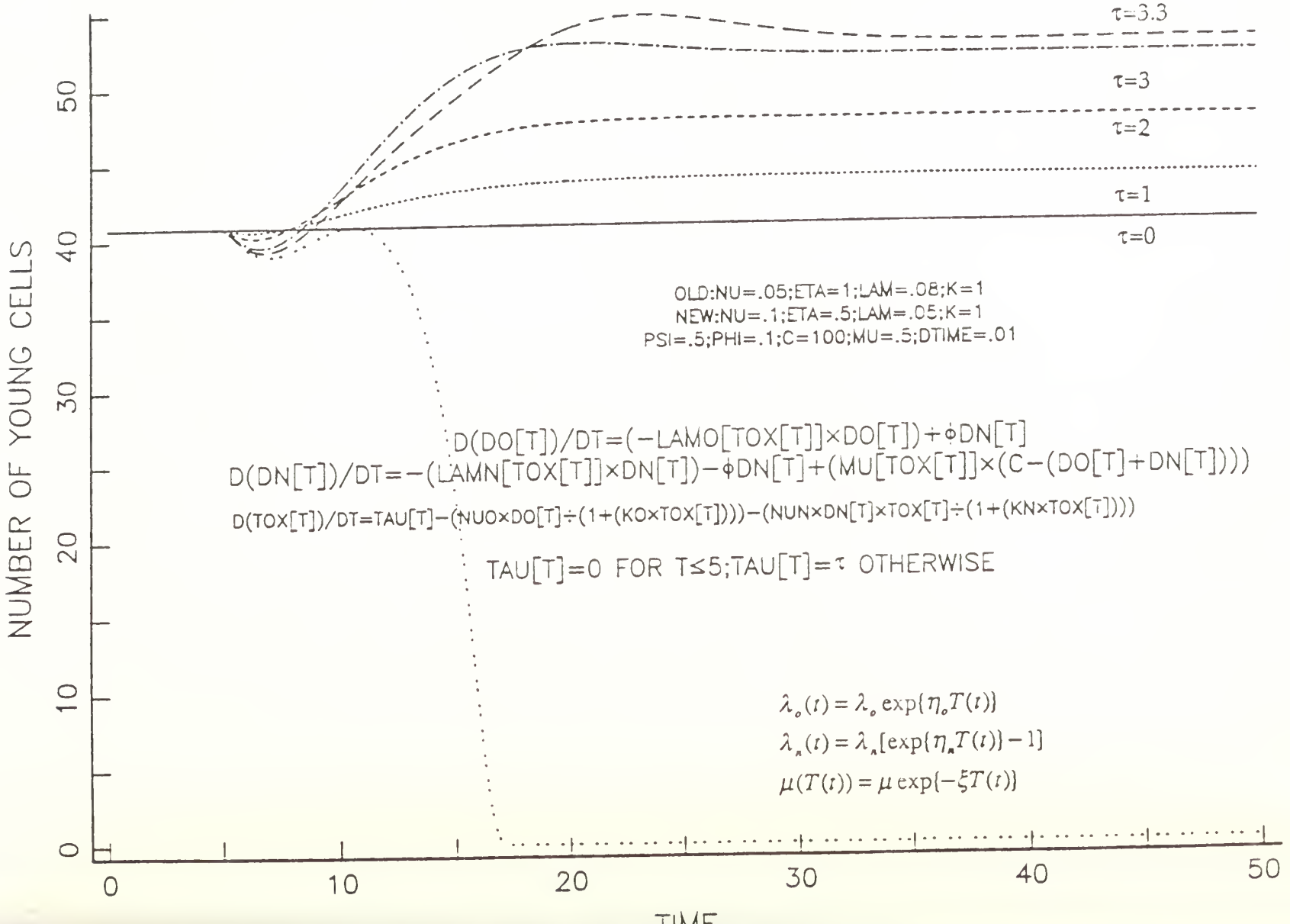


Figure 1


τ=3.3
τ=3
τ=2
τ=1
τ=0
OLD:NU=.05;ETA=1;LAM=.08;K=1
NEW:NU=.1;ETA=.5;LAM=.05;K=1
PSI=.5;PHI=.1;C=100;MU=.5;DTIME=.01
D(DO[T])/DT=(−LAMO[TOX[T]]×DO[T])+ϕDN[T]
D(DN[T])/DT=−(LAMN[TOX[T]]×DN[T])−ϕDN[T]+(MU[TOX[T]]×(C−(DO[T]+DN[T])))
D(TOX[T])/DT=TAU[T]−(NUO×DO[T]÷(1+(KO×TOX[T])))−(NUN×DN[T]×TOX[T]÷(1+(KN×TOX[T])))
TAU[T]=0 FOR T≤5;TAU[T]=τ OTHERWISE
$\lambda_o(t) = \lambda_o \exp\{\eta_o T(t)\}$
$\lambda_n(t) = \lambda_n[\exp\{\eta_n T(t)\} - 1]$
$\mu(T(t)) = \mu \exp\{-\xi T(t)\}$
NUMBER OF YOUNG CELLS
0
10
20
30
40
50
TIME

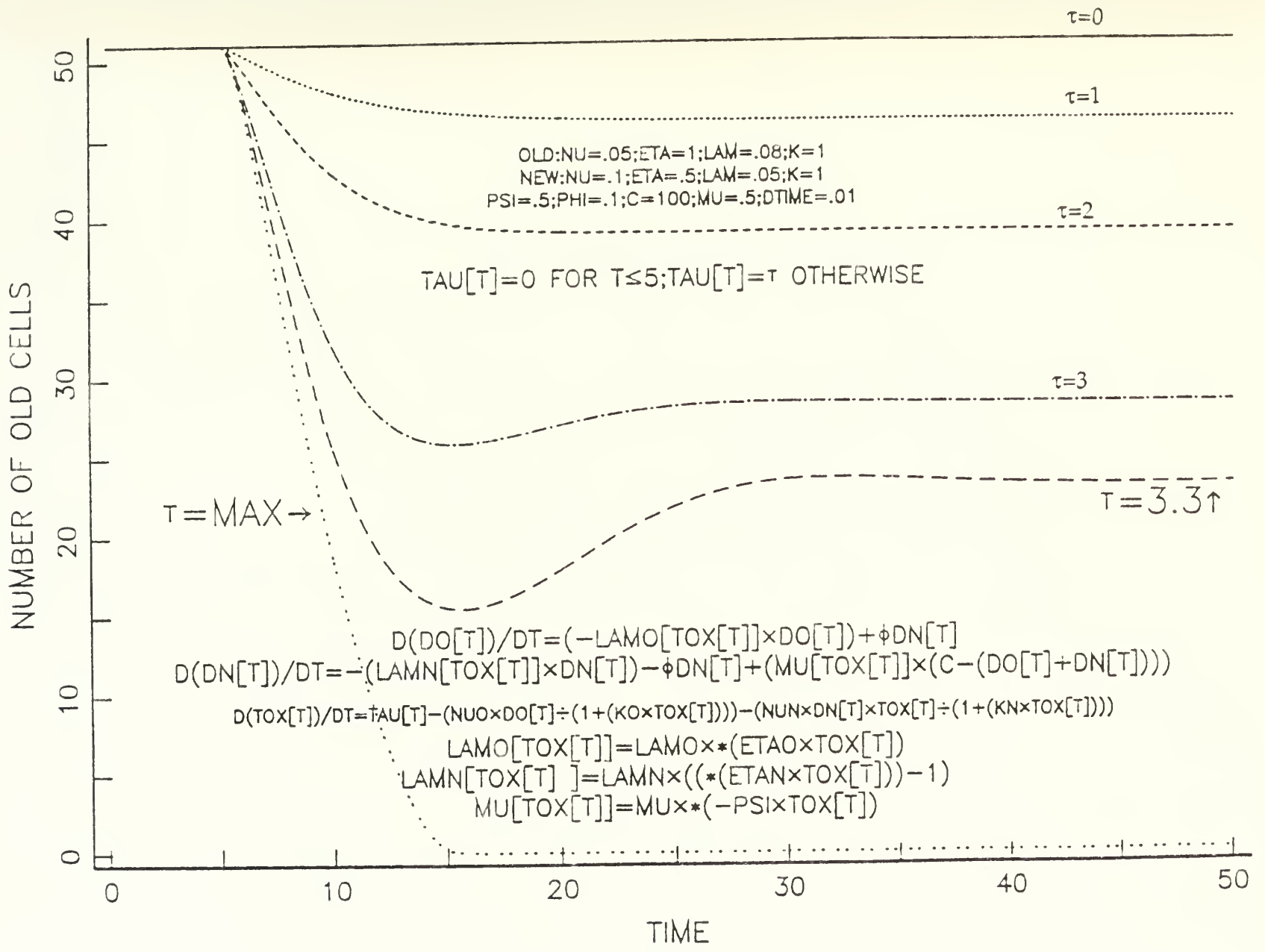
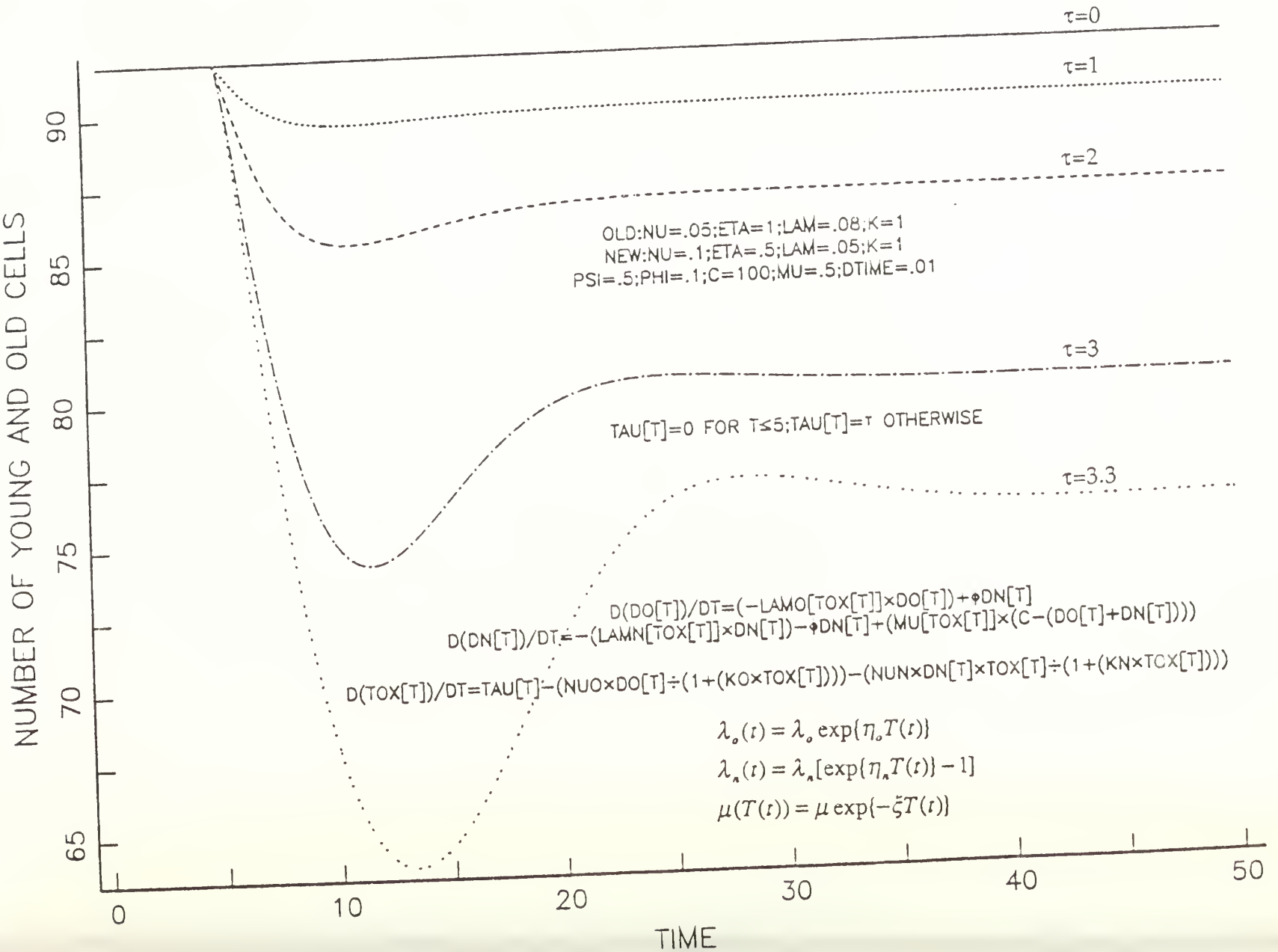

τ=0
τ=1
τ=2
τ=3
T=3.3↑
T=MAX→
OLD:NU=.05;ETA=1;LAM=.08;K=1
NEW:NU=.1;ETA=.5;LAM=.05;K=1
PSI=.5;PHI=.1;C=100;MU=.5;DTIME=.01
TAU[T]=0 FOR T≤5;TAU[T]=τ OTHERWISE
D(DO[T])/DT=(−LAMO[TOX[T]]×DO[T])+ϕDN[T]
D(DN[T])/DT=−(LAMN[TOX[T]]×DN[T])−ϕDN[T]+(MU[TOX[T]]×(C−(DO[T]+DN[T])))
D(TOX[T])/DT=TAU[T]−(NUO×DO[T]÷(1+(KO×TOX[T])))−(NUN×DN[T]×TOX[T]÷(1+(KN×TOX[T])))
LAMO[TOX[T]]=LAMO×*(ETAO×TOX[T])
LAMN[TOX[T]]=LAMN×((*(ETAN×TOX[T]))−1)
MU[TOX[T]]=MU×*(−PSI×TOX[T])
NUMBER OF OLD CELLS
0
10
20
30
40
50
TIME

Figure 3


τ=0
τ=1
τ=2
τ=3
τ=3.3
OLD:NU=.05;ETA=1;LAM=.08;K=1
NEW:NU=.1;ETA=.5;LAM=.05;K=1
PSI=.5;PHI=.1;C=100;MU=.5;DTIME=.01
TAU[T]=0 FOR T≤5;TAU[T]=τ OTHERWISE
D(DO[T])/DT=(−LAMO[TOX[T]]×DO[T])+φDN[T]
D(DN[T])/DT=−(LAMN[TOX[T]]×DN[T])−φDN[T]+(MU[TOX[T]]×(C−(DO[T]+DN[T])))
D(TOX[T])/DT=TAU[T]−(NUO×DO[T]÷(1+(KO×TOX[T])))−(NUN×DN[T]×TOX[T]÷(1+(KN×TOX[T])))
$\lambda_o(t) = \lambda_o \exp\{\eta_o T(t)\}$
$\lambda_n(t) = \lambda_n[\exp\{\eta_n T(t)\} - 1]$
$\mu(T(t)) = \mu \exp\{-\xi T(t)\}$
NUMBER OF YOUNG AND OLD CELLS
65
70
75
80
85
90
0
10
20
30
40
50
TIME

$$\lambda_o(t) = \lambda_o \exp\{\eta_o T(t)\}$$
$$\lambda_n(t) = \lambda_n[\exp\{\eta_n T(t)\} - 1]$$
$$\mu(T(t)) = \mu \exp\{-\xi T(t)\}$$

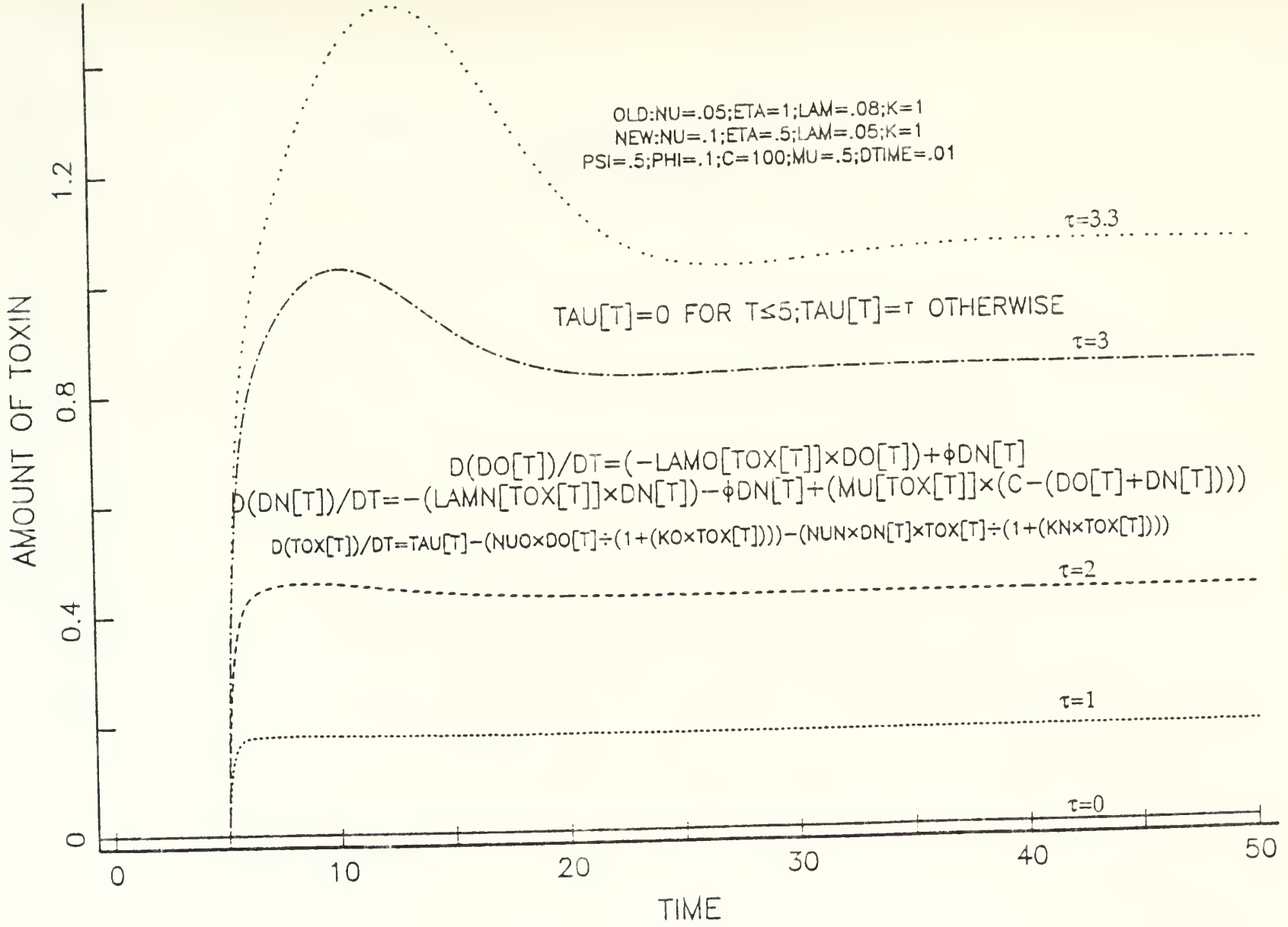
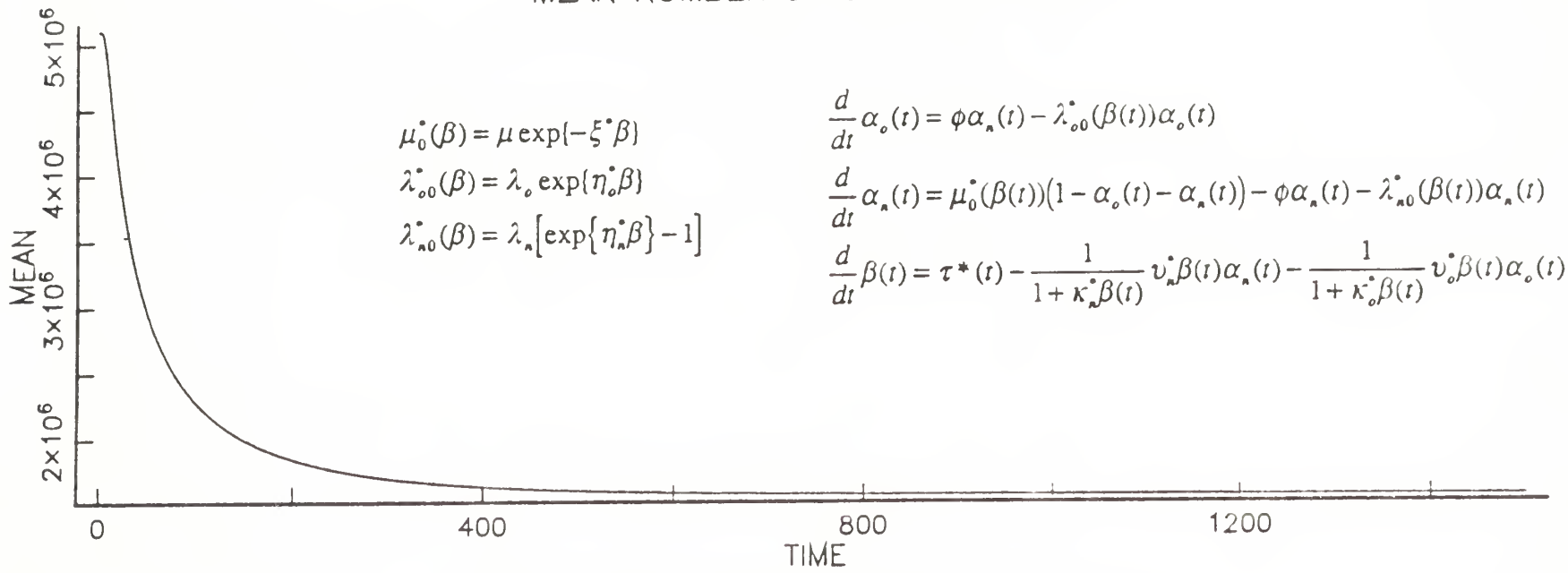


Figure 5

OLD CELL PAIRS

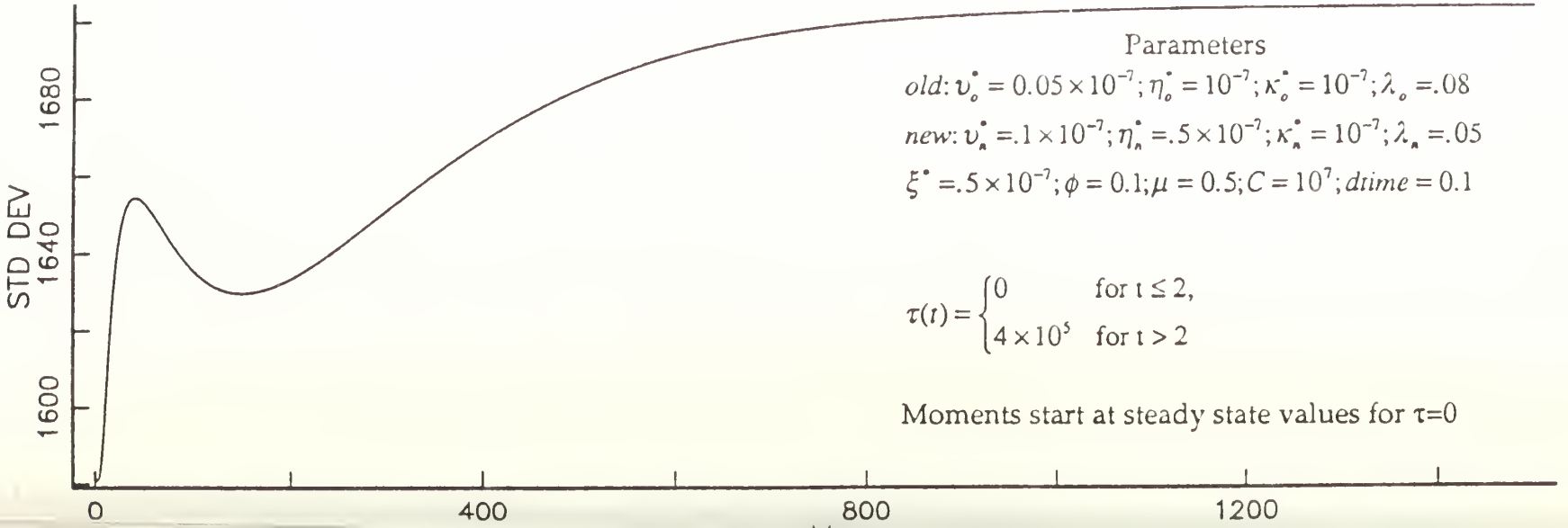
MEAN NUMBER OF OLD CELL PAIRS



$$\mu_0^*(\beta) = \mu \exp\{-\xi^*\beta\}$$
$$\lambda_{oo}^*(\beta) = \lambda_o \exp\{\eta_o^*\beta\}$$
$$\lambda_{no}^*(\beta) = \lambda_n\left[\exp\{\eta_n^*\beta\} - 1\right]$$

$$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{oo}^*(\beta(t))\alpha_o(t)$$
$$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1 - \alpha_o(t) - \alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{no}^*(\beta(t))\alpha_n(t)$$
$$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$$

STD DEV OF NUMBER OF OLD CELL PAIRS



Parameters

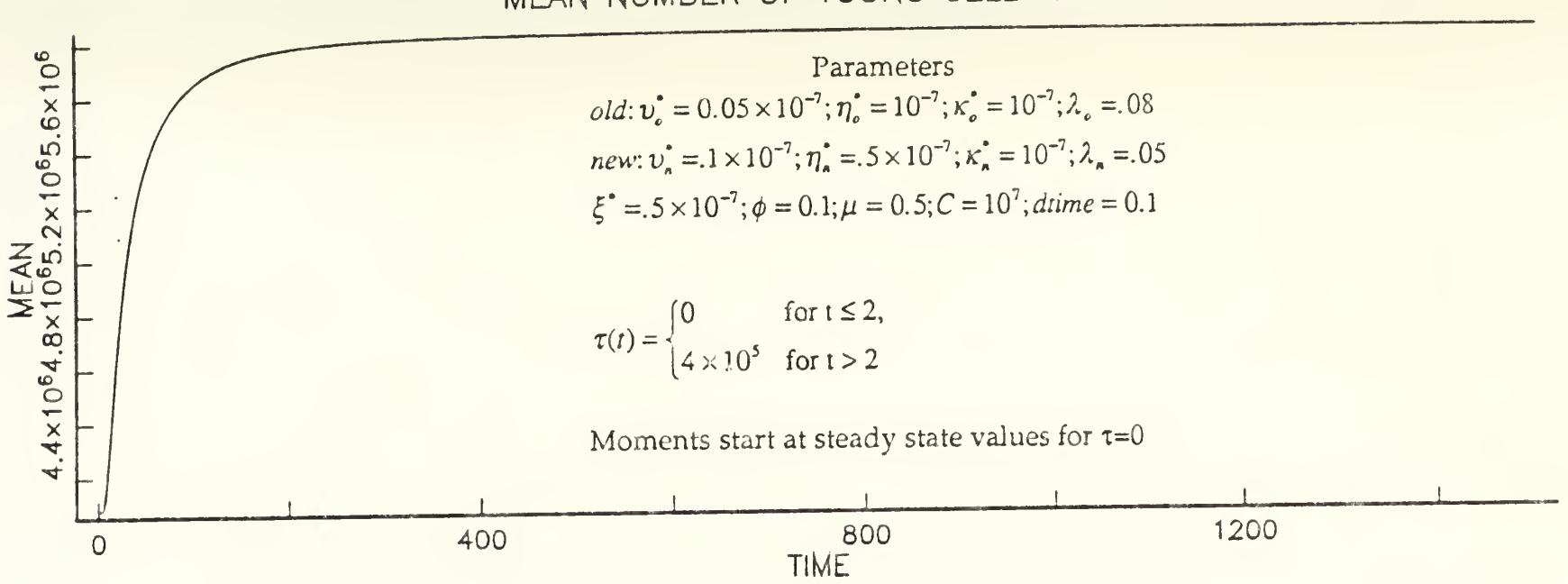
old: $\upsilon_o^* = 0.05\times10^{-7}; \eta_o^* = 10^{-7}; \kappa_o^* = 10^{-7}; \lambda_o = .08$

new: $\upsilon_n^* = .1\times10^{-7}; \eta_n^* = .5\times10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$

$\xi^* = .5\times10^{-7}; \phi = 0.1; \mu = 0.5; C = 10^7; dtime = 0.1$

$$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 4\times10^5 & \text{for } t > 2 \end{cases}$$

Moments start at steady state values for τ=0


MEAN NUMBER OF YOUNG CELL PAIRS
MEAN
4.4×10^6 4.8×10^6 5.2×10^6 5.6×10^6
0
400
800
1200
TIME
Parameters
old: $\upsilon_o^* = 0.05\times10^{-7}; \eta_o^* = 10^{-7}; \kappa_o^* = 10^{-7}; \lambda_o = .08$
new: $\upsilon_n^* = .1\times10^{-7}; \eta_n^* = .5\times10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$
$\xi^* = .5\times10^{-7}; \phi = 0.1; \mu = 0.5; C = 10^7; dtime = 0.1$
$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 4\times10^5 & \text{for } t > 2 \end{cases}$
Moments start at steady state values for τ=0

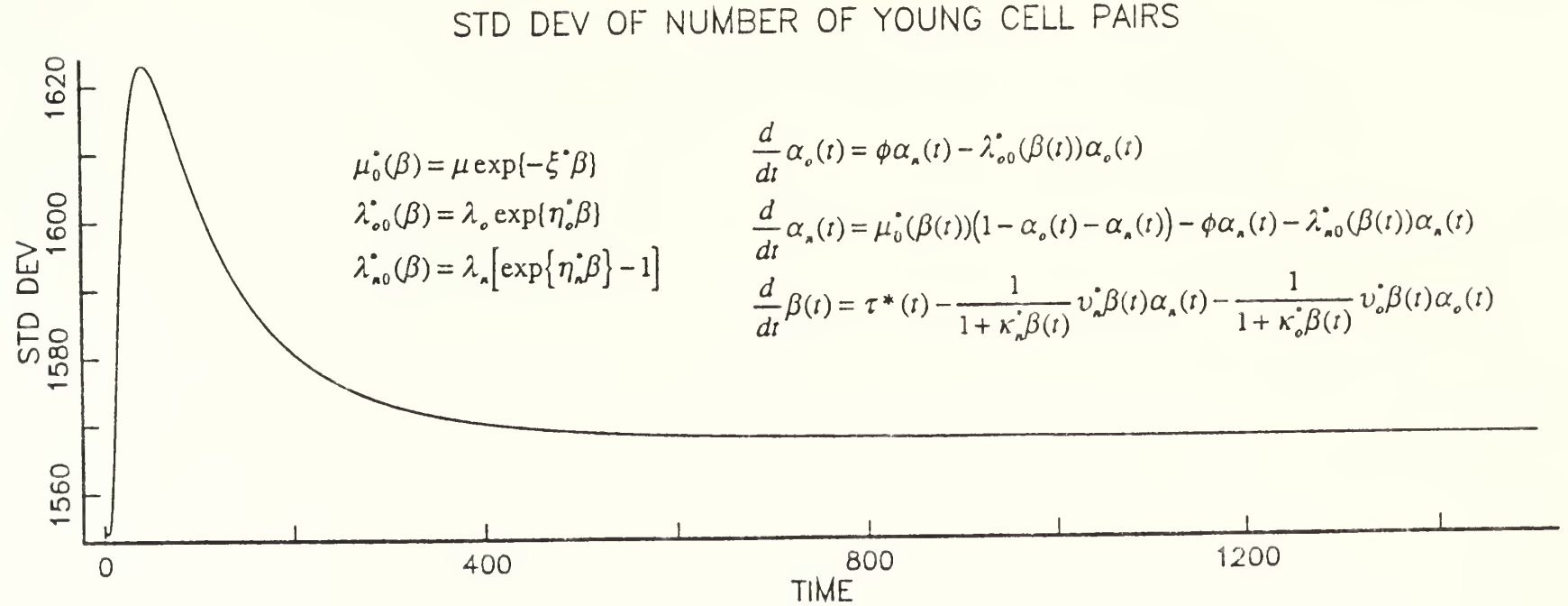
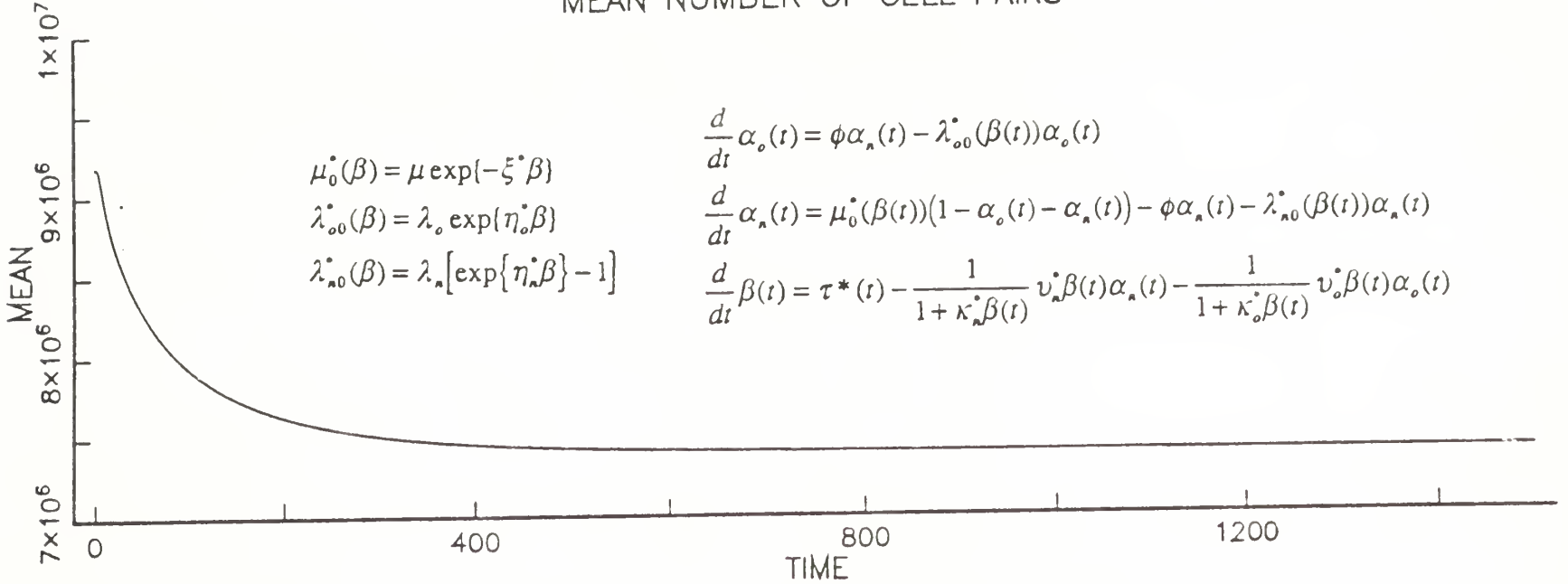

STD DEV OF NUMBER OF YOUNG CELL PAIRS
STD DEV
1560 1580 1600 1620
0
400
800
1200
TIME
$\mu_0^*(\beta) = \mu\exp\{-\xi^*\beta\}$
$\lambda_{oo}^*(\beta) = \lambda_o\exp\{\eta_o^*\beta\}$
$\lambda_{no}^*(\beta) = \lambda_n\left[\exp\{\eta_n^*\beta\} - 1\right]$
$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{oo}^*(\beta(t))\alpha_o(t)$
$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1-\alpha_o(t)-\alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{no}^*(\beta(t))\alpha_n(t)$
$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$

Figure 7

TOTALLY DIFFERENTIATED CELL PAIRS

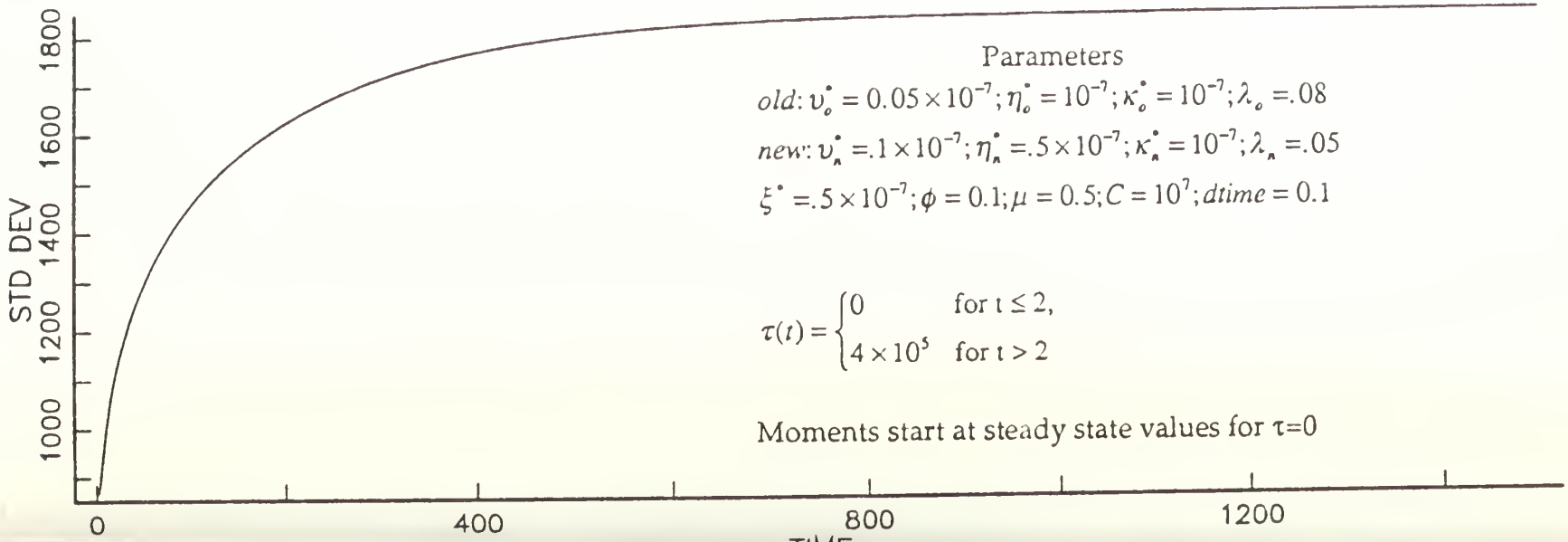
MEAN NUMBER OF CELL PAIRS



$$\mu_0^*(\beta) = \mu \exp\{-\xi^* \beta\}$$
$$\lambda_{oo}^*(\beta) = \lambda_o \exp\{\eta_o^* \beta\}$$
$$\lambda_{no}^*(\beta) = \lambda_n \left[\exp\{\eta_n^* \beta\} - 1\right]$$

$$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{oo}^*(\beta(t))\alpha_o(t)$$
$$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1 - \alpha_o(t) - \alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{no}^*(\beta(t))\alpha_n(t)$$
$$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$$

STD DEV OF NUMBER OF CELL PAIRS



Parameters

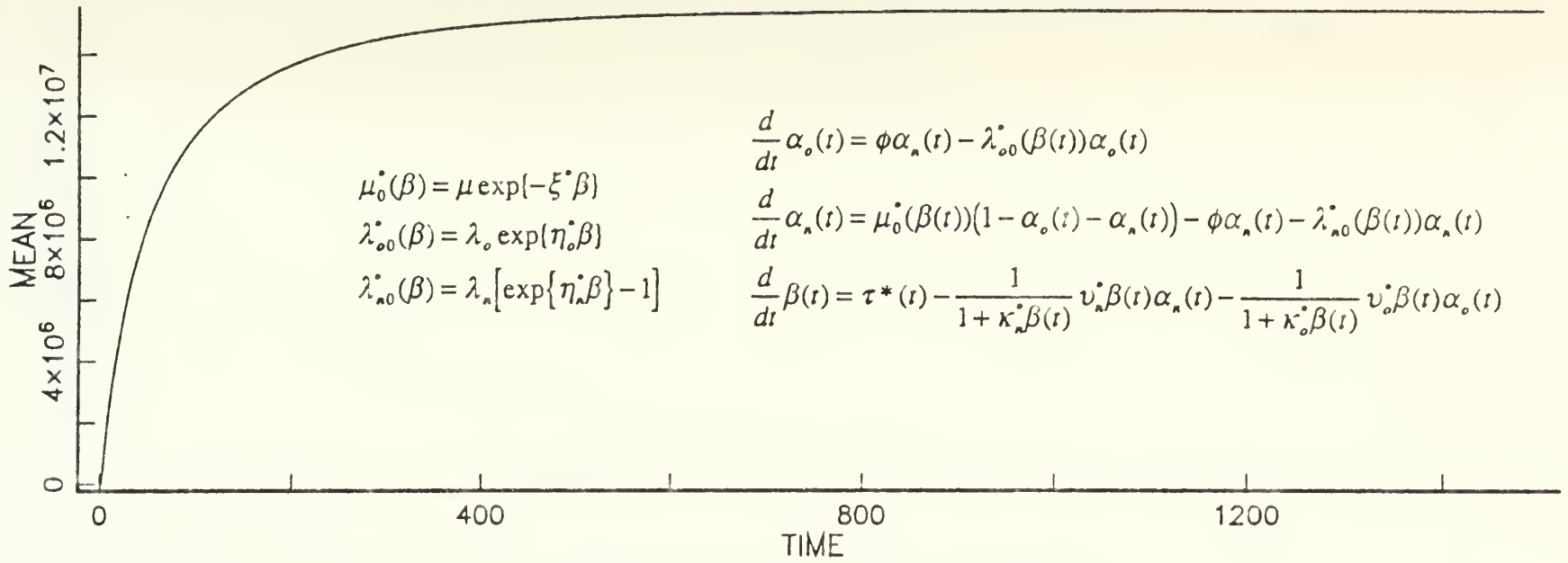
old: $\upsilon_o^* = 0.05 \times 10^{-7}; \eta_o^* = 10^{-7}; \kappa_o^* = 10^{-7}; \lambda_o = .08$

new: $\upsilon_n^* = .1 \times 10^{-7}; \eta_n^* = .5 \times 10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$

$\xi^* = .5 \times 10^{-7}; \phi = 0.1; \mu = 0.5; C = 10^7; dtime = 0.1$

$$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 4 \times 10^5 & \text{for } t > 2 \end{cases}$$

Moments start at steady state values for τ=0


MEAN AMOUNT OF TOXIN
MEAN
0
4×10^6
8×10^6
1.2×10^7
0
400
800
1200
TIME
$\mu_0^*(\beta) = \mu \exp\{-\xi^* \beta\}$
$\lambda_{o0}^*(\beta) = \lambda_o \exp\{\eta_o^* \beta\}$
$\lambda_{n0}^*(\beta) = \lambda_n \left[\exp\{\eta_n^* \beta\} - 1\right]$
$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{o0}^*(\beta(t))\alpha_o(t)$
$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))(1 - \alpha_o(t) - \alpha_n(t)) - \phi\alpha_n(t) - \lambda_{n0}^*(\beta(t))\alpha_n(t)$
$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$

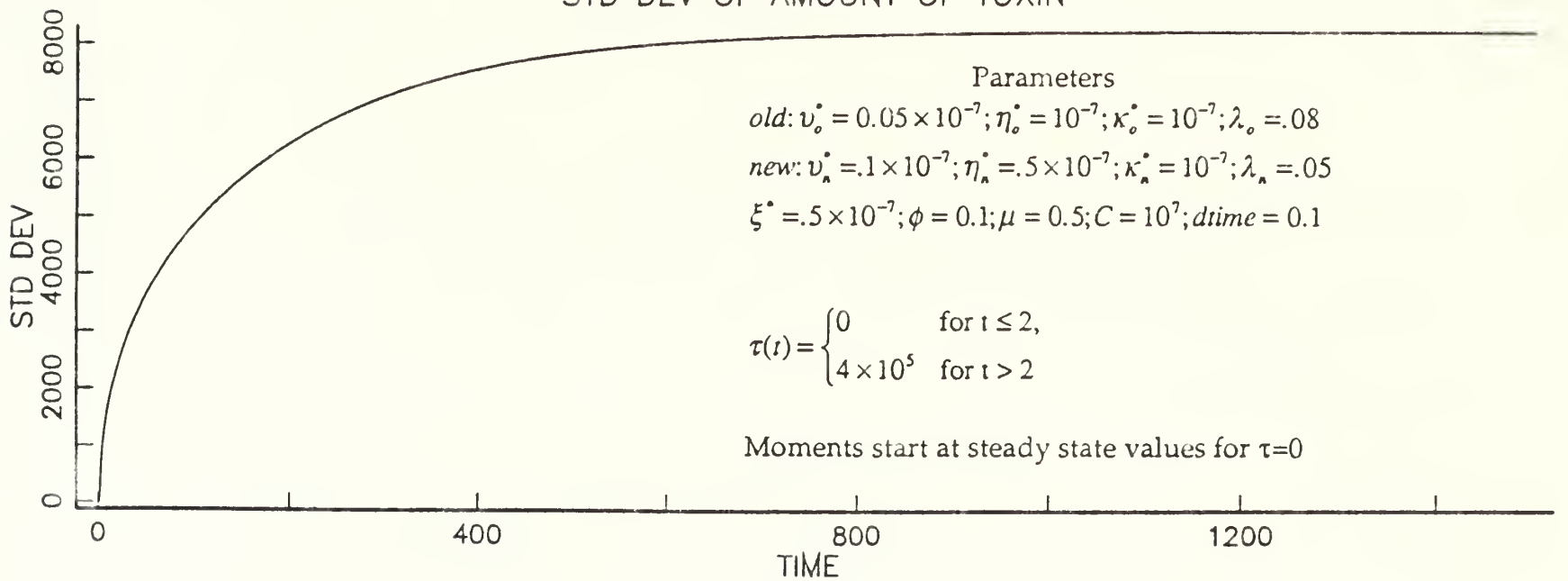
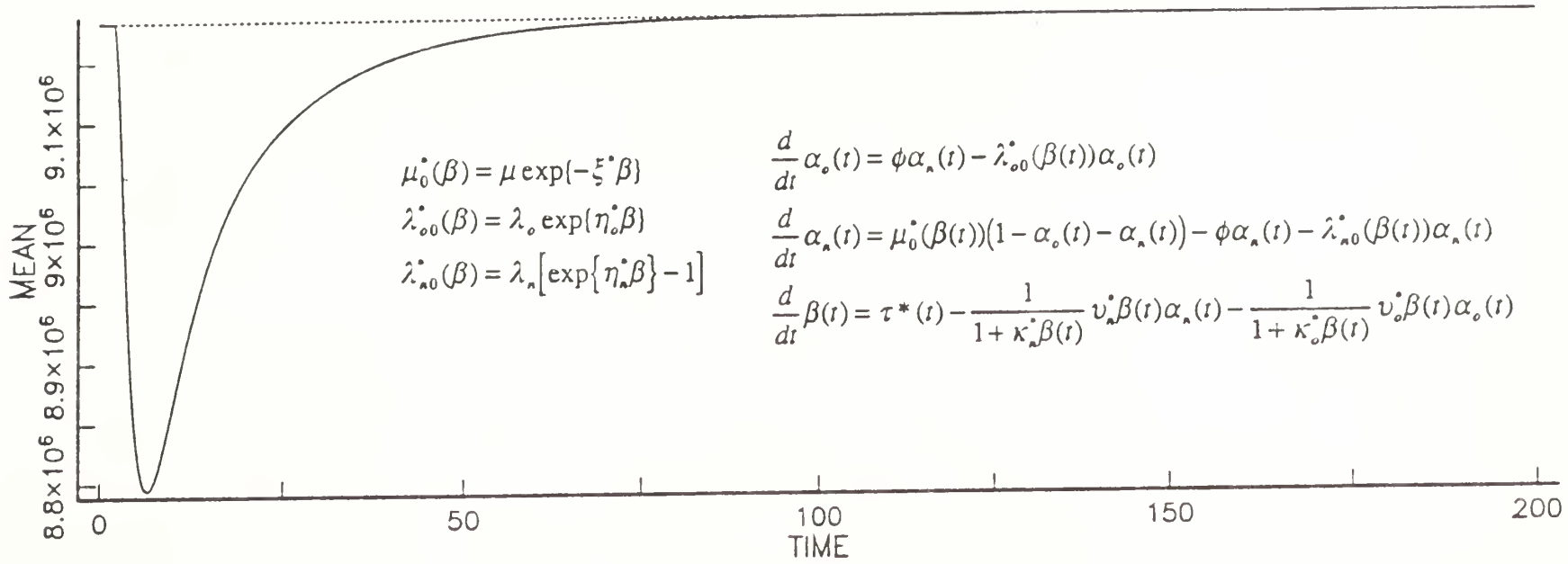

STD DEV OF AMOUNT OF TOXIN
STD DEV
0
2000
4000
6000
8000
0
400
800
1200
TIME
Parameters
old: $\upsilon_o^* = 0.05 \times 10^{-7}; \eta_o^* = 10^{-7}; \kappa_o^* = 10^{-7}; \lambda_o = .08$
new: $\upsilon_n^* = .1 \times 10^{-7}; \eta_n^* = .5 \times 10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$
$\xi^* = .5 \times 10^{-7}; \phi = 0.1; \mu = 0.5; C = 10^7; dtime = 0.1$
$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 4 \times 10^5 & \text{for } t > 2 \end{cases}$
Moments start at steady state values for τ=0

Figure 9

TOTALLY DIFFERENTIATED CELL PAIRS

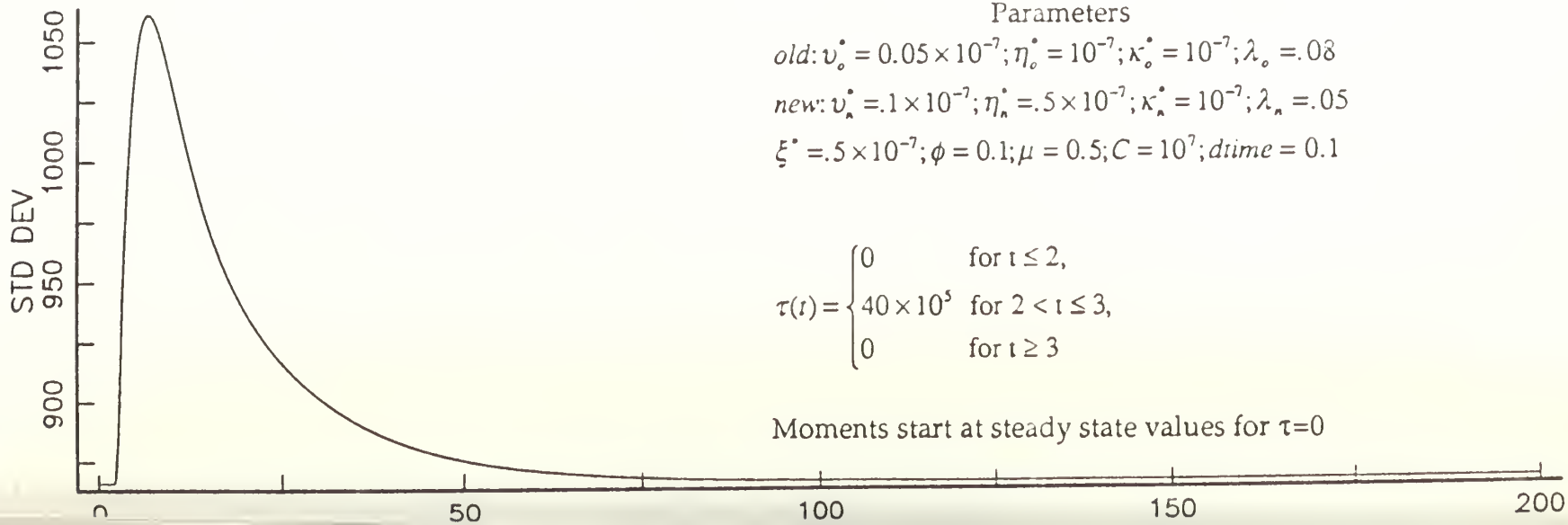
MEAN NUMBER OF CELL PAIRS



$$\mu_0^*(\beta) = \mu \exp\{-\xi^*\beta\}$$
$$\lambda_{00}^*(\beta) = \lambda_0 \exp\{\eta_0^*\beta\}$$
$$\lambda_{n0}^*(\beta) = \lambda_n\left[\exp\{\eta_n^*\beta\} - 1\right]$$

$$\frac{d}{dt}\alpha_0(t) = \phi\alpha_n(t) - \lambda_{00}^*(\beta(t))\alpha_0(t)$$
$$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1 - \alpha_0(t) - \alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{n0}^*(\beta(t))\alpha_n(t)$$
$$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_0^*\beta(t)}\upsilon_0^*\beta(t)\alpha_0(t)$$

STD DEV OF NUMBER OF CELL PAIRS



Parameters

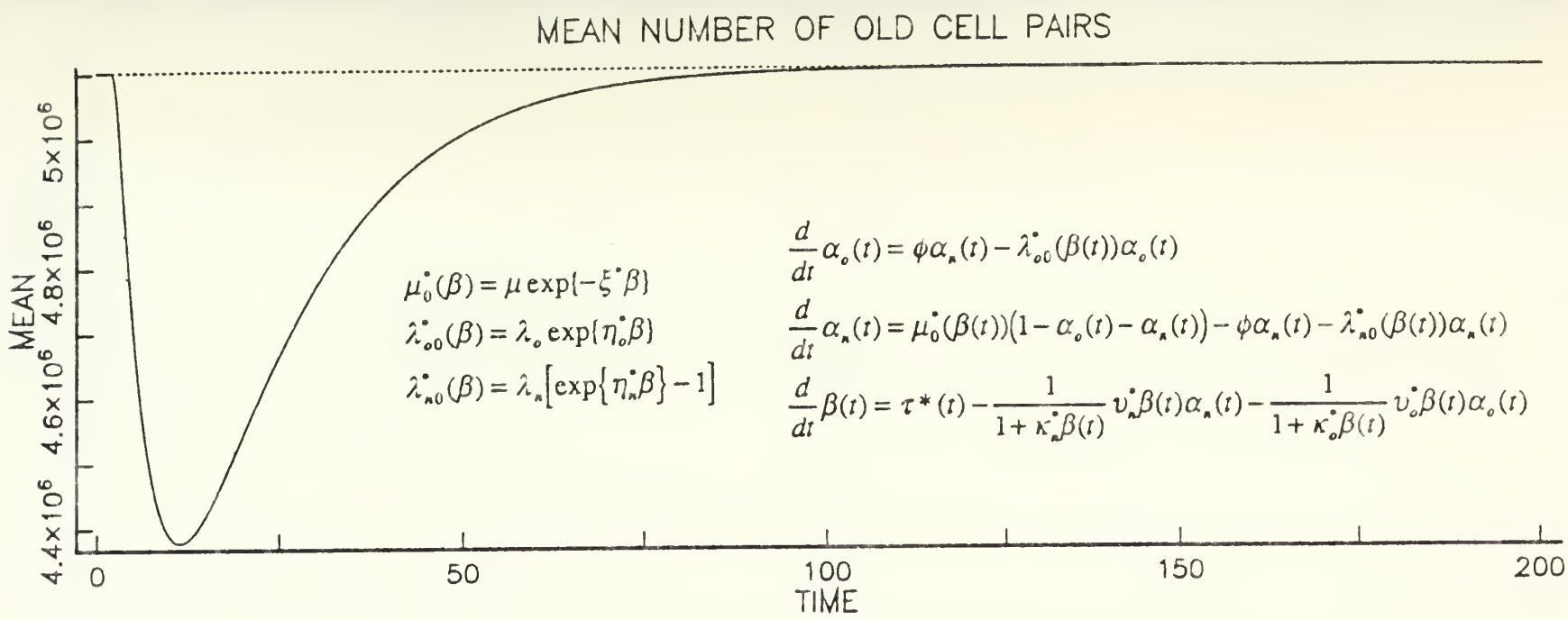
$old: \upsilon_0^* = 0.05\times10^{-7}; \eta_0^* = 10^{-7}; \kappa_0^* = 10^{-7}; \lambda_0 = .08$

$new: \upsilon_n^* = .1\times10^{-7}; \eta_n^* = .5\times10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$

$\xi^* = .5\times10^{-7}; \phi = 0.1; \mu = 0.5; C = 10^7; dtime = 0.1$

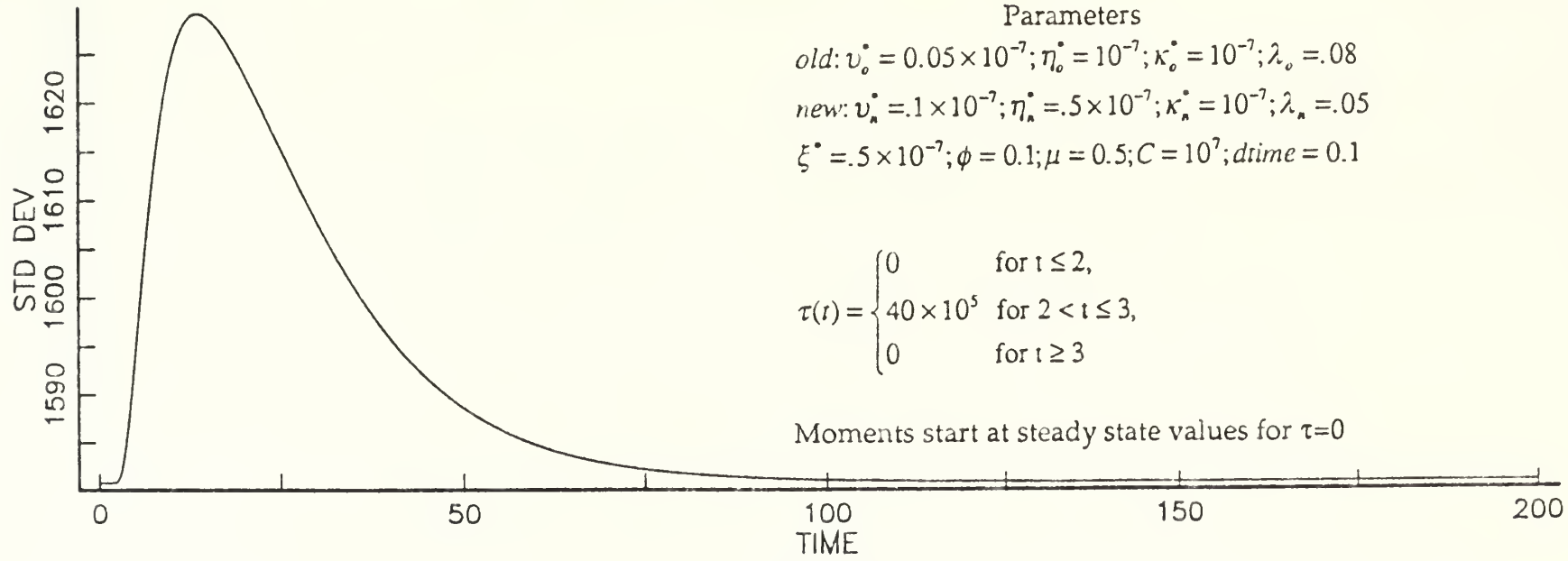
$$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 40\times10^5 & \text{for } 2 < t \le 3, \\ 0 & \text{for } t \ge 3 \end{cases}$$

Moments start at steady state values for τ=0



$$\mu_0^*(\beta) = \mu \exp\{-\xi^* \beta\}$$
$$\lambda_{00}^*(\beta) = \lambda_0 \exp\{\eta_0^* \beta\}$$
$$\lambda_{n0}^*(\beta) = \lambda_n \left[\exp\{\eta_n^* \beta\} - 1\right]$$

$$\frac{d}{dt}\alpha_0(t) = \phi\alpha_n(t) - \lambda_{00}^*(\beta(t))\alpha_0(t)$$
$$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1 - \alpha_0(t) - \alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{n0}^*(\beta(t))\alpha_n(t)$$
$$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_0^*\beta(t)}\upsilon_0^*\beta(t)\alpha_0(t)$$



Parameters

old: $\upsilon_0^* = 0.05 \times 10^{-7}; \eta_0^* = 10^{-7}; \kappa_0^* = 10^{-7}; \lambda_0 = .08$

new: $\upsilon_n^* = .1 \times 10^{-7}; \eta_n^* = .5 \times 10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$

$\xi^* = .5 \times 10^{-7}; \phi = 0.1; \mu = 0.5; C = 10^7; dtime = 0.1$

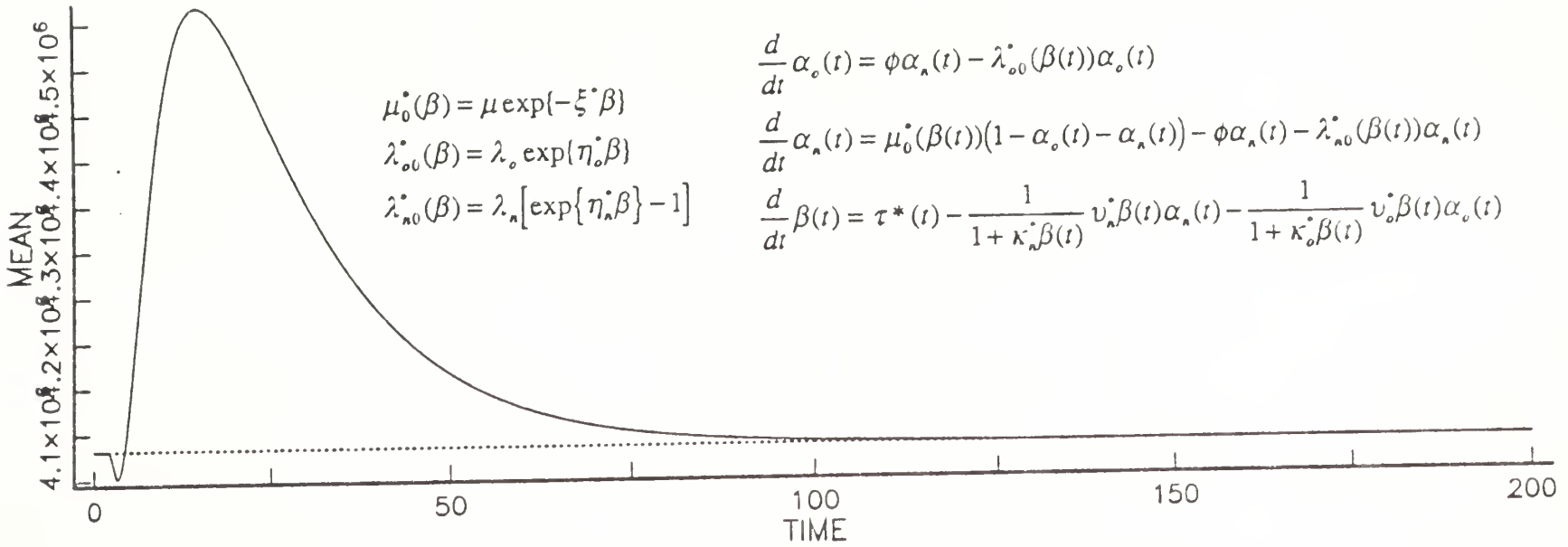
$$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 40 \times 10^5 & \text{for } 2 < t \le 3, \\ 0 & \text{for } t \ge 3 \end{cases}$$

Moments start at steady state values for τ=0

Figure 11

YOUNG CELL PAIRS

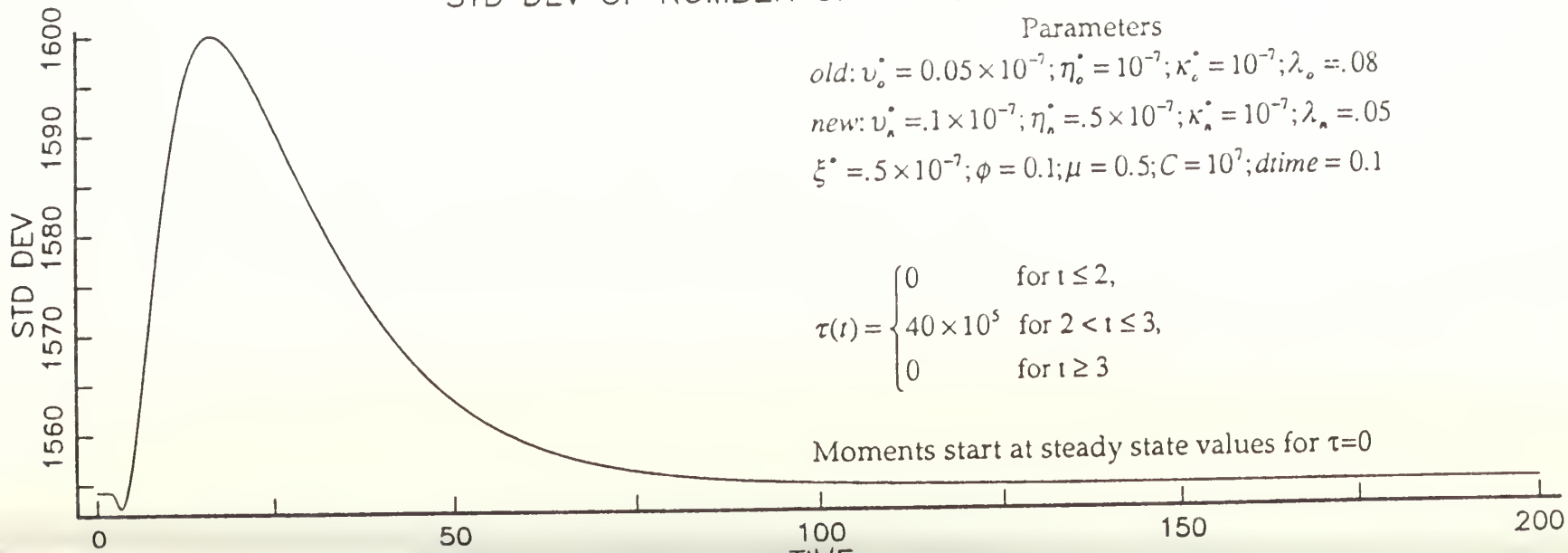
MEAN NUMBER OF YOUNG CELL PAIRS



$$\mu_0^*(\beta) = \mu \exp\{-\xi^* \beta\}$$
$$\lambda_{o0}^*(\beta) = \lambda_o \exp\{\eta_o^* \beta\}$$
$$\lambda_{n0}^*(\beta) = \lambda_n\left[\exp\{\eta_n^* \beta\} - 1\right]$$

$$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{o0}^*(\beta(t))\alpha_o(t)$$
$$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1 - \alpha_o(t) - \alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{n0}^*(\beta(t))\alpha_n(t)$$
$$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$$

STD DEV OF NUMBER OF YOUNG CELL PAIRS



Parameters

old: $\upsilon_o^* = 0.05\times10^{-7}; \eta_o^* = 10^{-7}; \kappa_o^* = 10^{-7}; \lambda_o = .08$

new: $\upsilon_n^* = .1\times10^{-7}; \eta_n^* = .5\times10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$

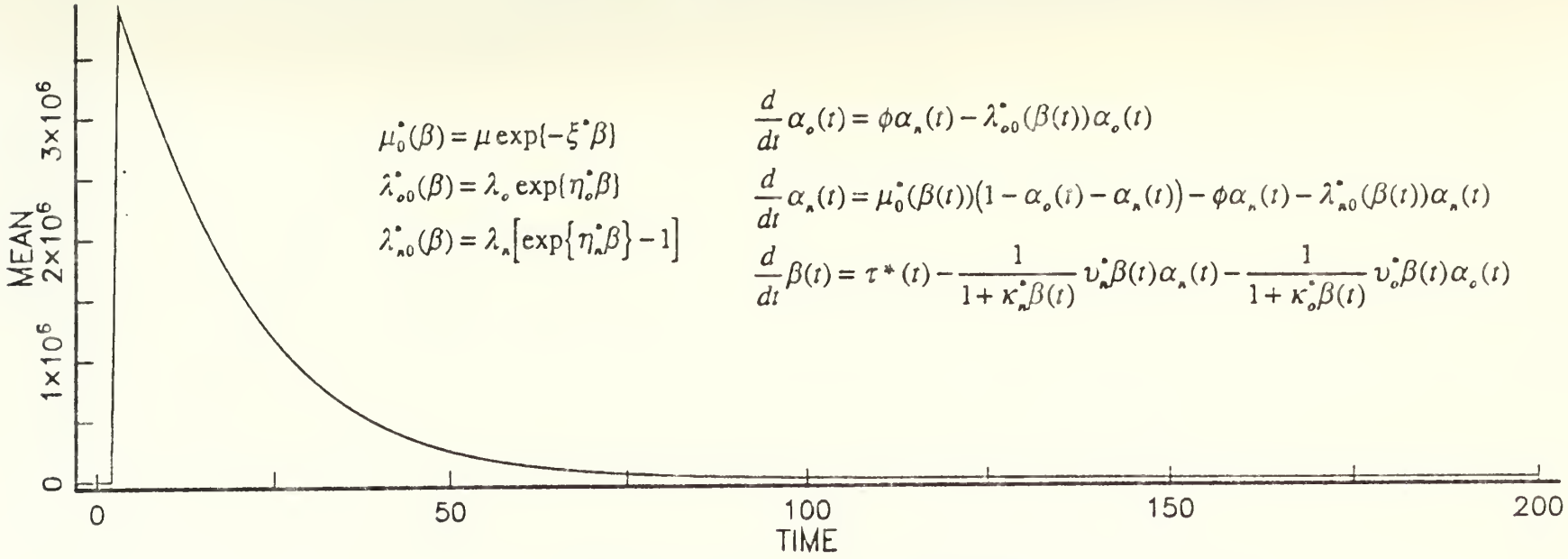
$\xi^* = .5\times10^{-7}; \phi = 0.1; \mu = 0.5; C = 10^7; dtime = 0.1$

$$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 40\times10^5 & \text{for } 2 < t \le 3, \\ 0 & \text{for } t \ge 3 \end{cases}$$

Moments start at steady state values for τ=0

AMOUNT OF TOXIN

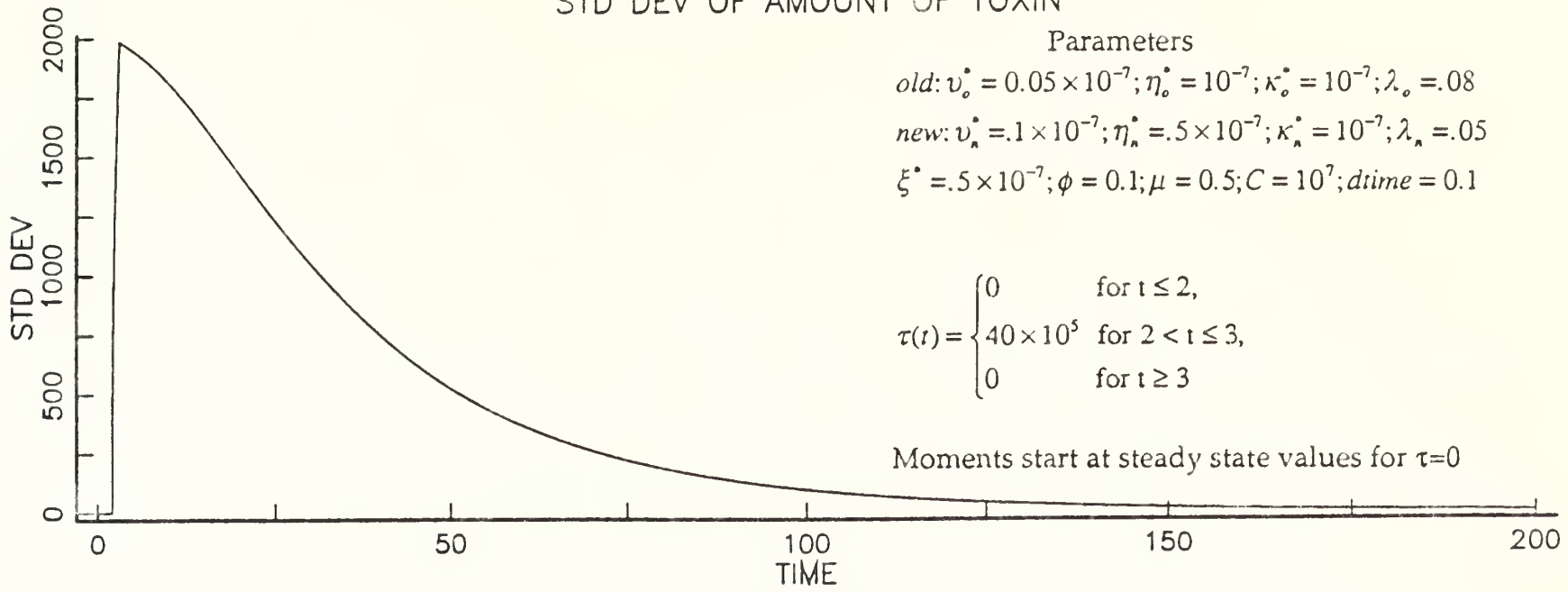
MEAN AMOUNT OF TOXIN



$$\mu_0^*(\beta) = \mu \exp\{-\xi^*\beta\}$$
$$\lambda_{o0}^*(\beta) = \lambda_o \exp\{\eta_o^*\beta\}$$
$$\lambda_{n0}^*(\beta) = \lambda_n\left[\exp\{\eta_n^*\beta\} - 1\right]$$

$$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{o0}^*(\beta(t))\alpha_o(t)$$
$$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1 - \alpha_o(t) - \alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{n0}^*(\beta(t))\alpha_n(t)$$
$$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$$

STD DEV OF AMOUNT OF TOXIN



Parameters

old: $\upsilon_o^* = 0.05\times10^{-7}; \eta_o^* = 10^{-7}; \kappa_o^* = 10^{-7}; \lambda_o = .08$

new: $\upsilon_n^* = .1\times10^{-7}; \eta_n^* = .5\times10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$

$\xi^* = .5\times10^{-7}; \phi = 0.1; \mu = 0.5; C = 10^7; dtime = 0.1$

$$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 40\times10^5 & \text{for } 2 < t \le 3, \\ 0 & \text{for } t \ge 3 \end{cases}$$

Moments start at steady state values for τ=0

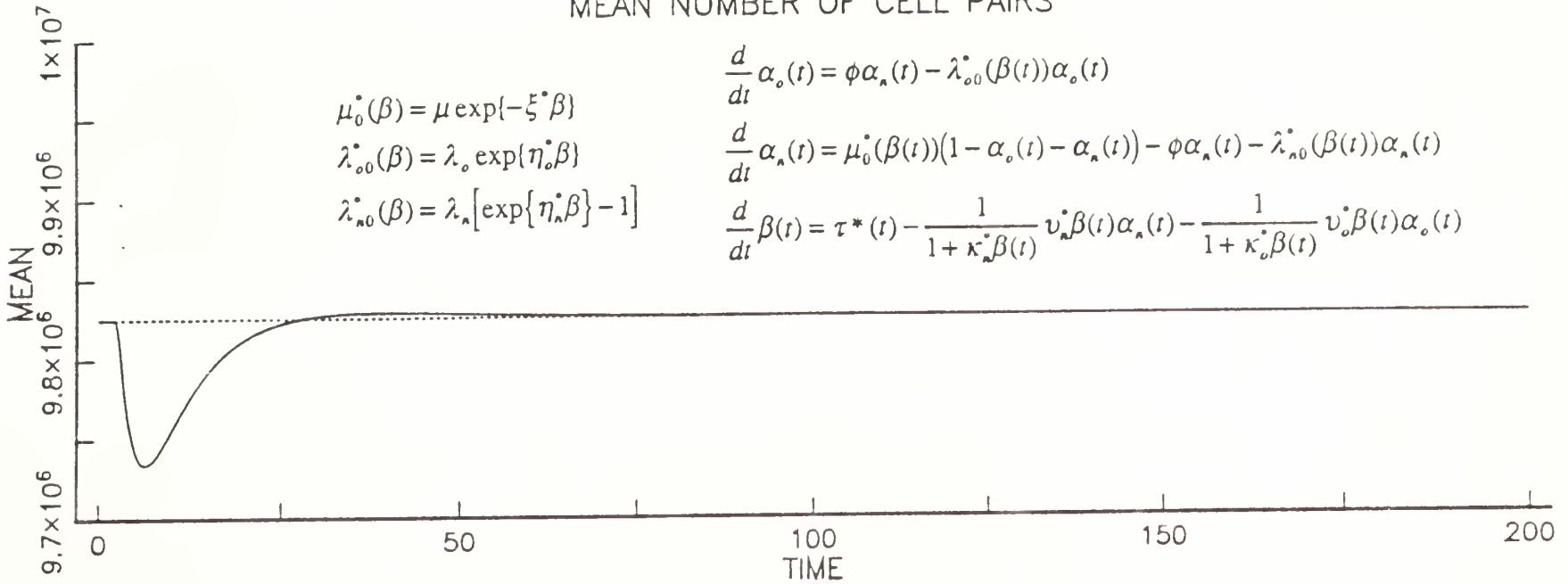
Figure 13

TOTALLY DIFFERENTIATED CELL PAIRS

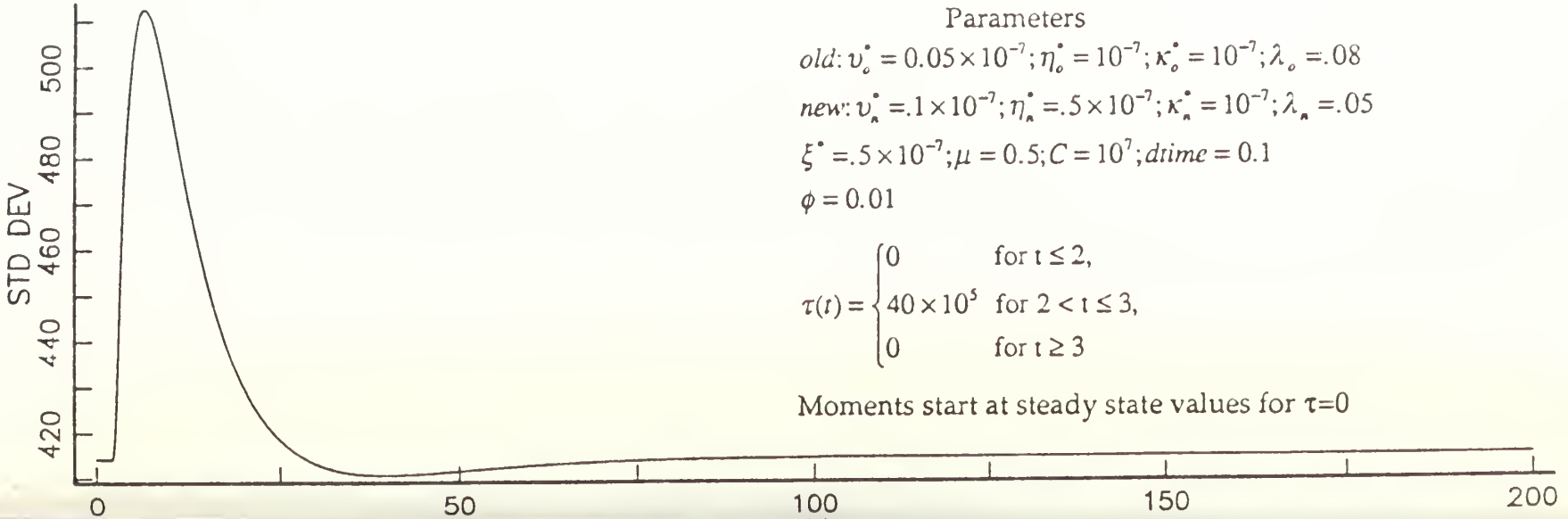
MEAN NUMBER OF CELL PAIRS

$$\mu_0^*(\beta) = \mu \exp\{-\xi^* \beta\}$$
$$\lambda_{o0}^*(\beta) = \lambda_o \exp\{\eta_o^* \beta\}$$
$$\lambda_{n0}^*(\beta) = \lambda_n \left[\exp\{\eta_n^* \beta\} - 1\right]$$

$$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{o0}^*(\beta(t))\alpha_o(t)$$
$$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1 - \alpha_o(t) - \alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{n0}^*(\beta(t))\alpha_n(t)$$
$$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$$



STD DEV OF NUMBER OF CELL PAIRS



Parameters

old: $\upsilon_o^* = 0.05\times10^{-7}; \eta_o^* = 10^{-7}; \kappa_o^* = 10^{-7}; \lambda_o = .08$

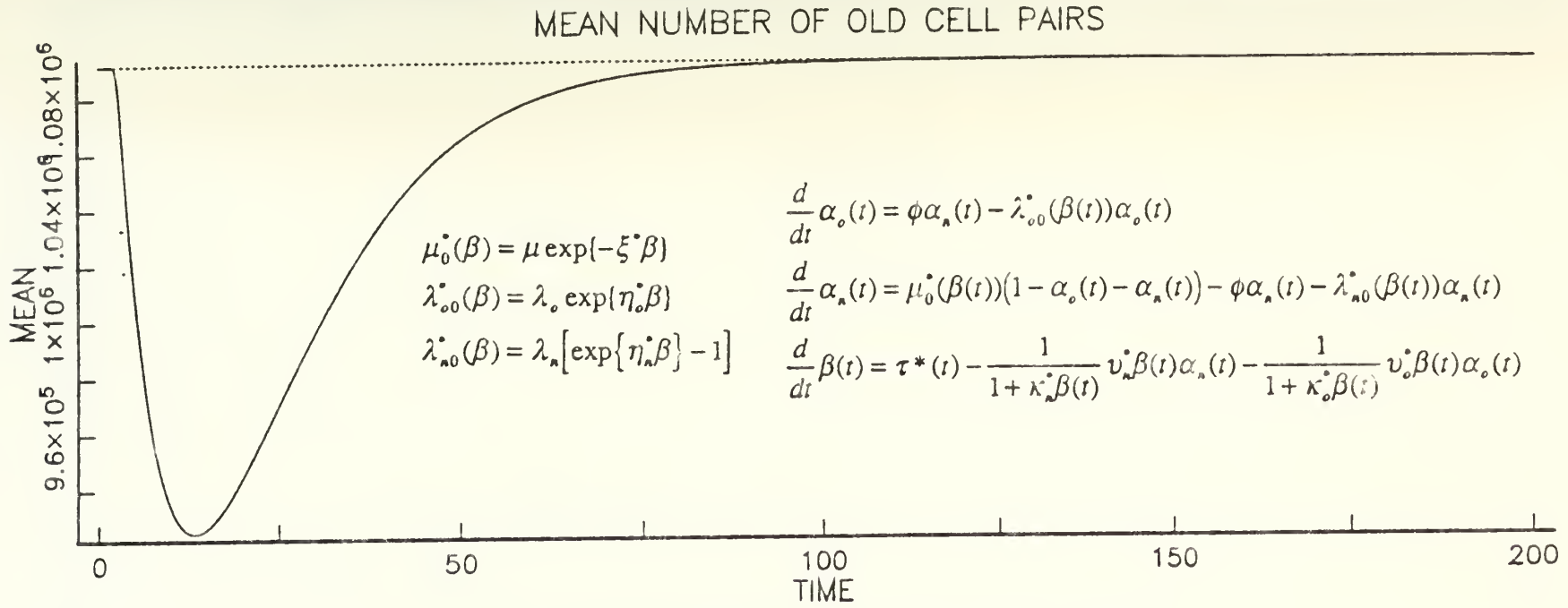
new: $\upsilon_n^* = .1\times10^{-7}; \eta_n^* = .5\times10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$

$\xi^* = .5\times10^{-7}; \mu = 0.5; C = 10^7; dtime = 0.1$

$\phi = 0.01$

$$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 40\times10^5 & \text{for } 2 < t \le 3, \\ 0 & \text{for } t \ge 3 \end{cases}$$

Moments start at steady state values for τ=0


MEAN NUMBER OF OLD CELL PAIRS
MEAN
9.6×10^5
1×10^6
1.04×10^6
1.08×10^6
0
50
100
150
200
TIME
$\mu_0^*(\beta) = \mu \exp\{-\xi^* \beta\}$
$\lambda_{o0}^*(\beta) = \lambda_o \exp\{\eta_o^* \beta\}$
$\lambda_{n0}^*(\beta) = \lambda_n \left[\exp\{\eta_n^* \beta\} - 1\right]$
$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{o0}^*(\beta(t))\alpha_o(t)$
$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))(1 - \alpha_o(t) - \alpha_n(t)) - \phi\alpha_n(t) - \lambda_{n0}^*(\beta(t))\alpha_n(t)$
$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$

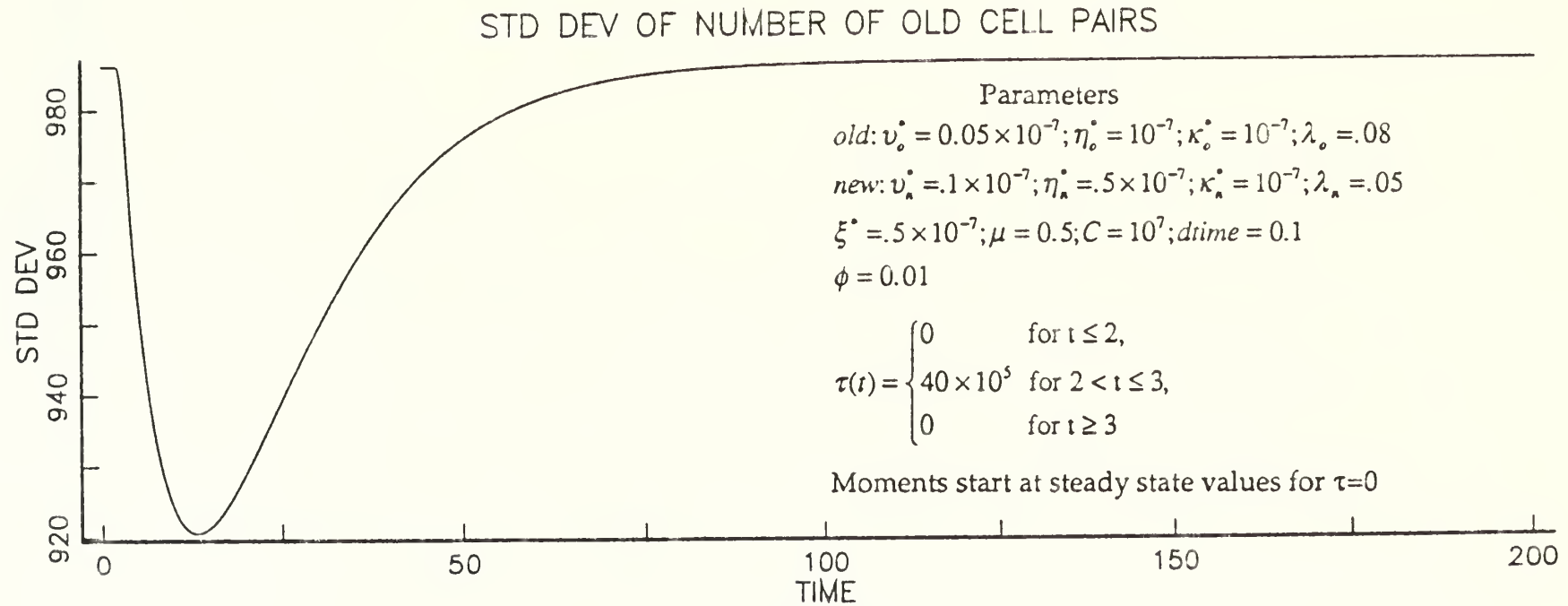
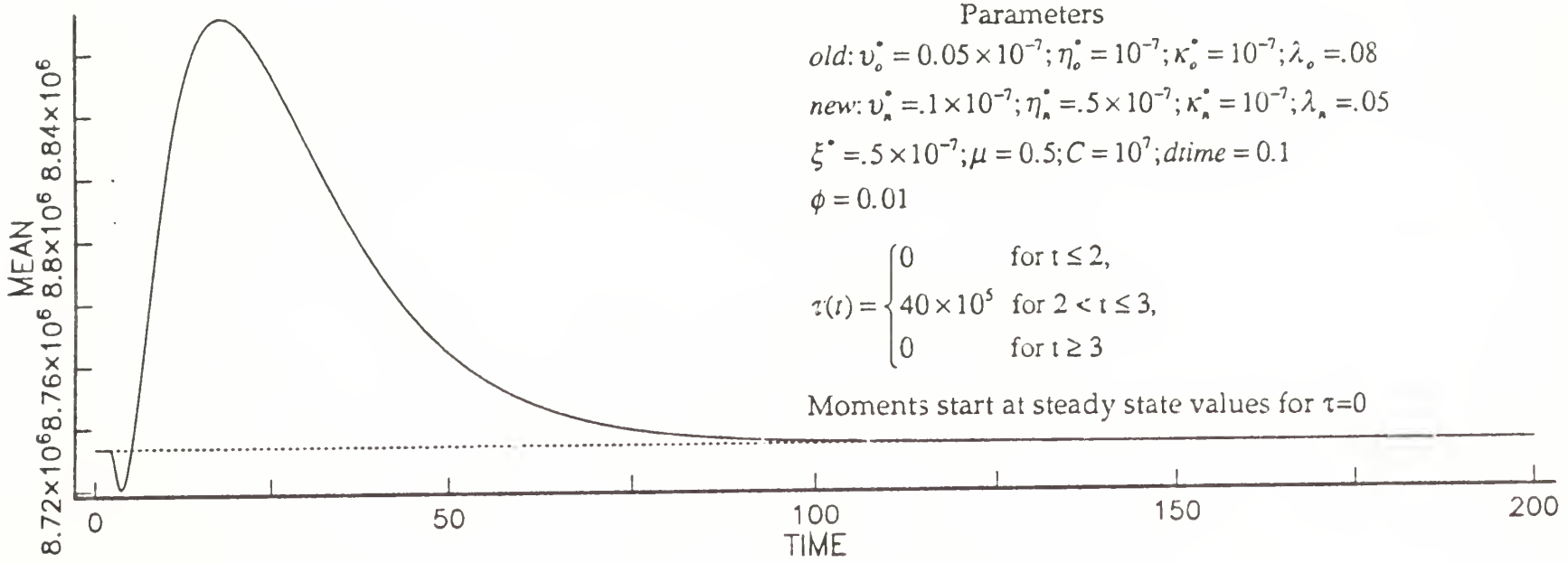

STD DEV OF NUMBER OF OLD CELL PAIRS
STD DEV
920
940
960
980
0
50
100
150
200
TIME
Parameters
$old: \upsilon_o^* = 0.05\times10^{-7}; \eta_o^* = 10^{-7}; \kappa_o^* = 10^{-7}; \lambda_o = .08$
$new: \upsilon_n^* = .1\times10^{-7}; \eta_n^* = .5\times10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$
$\xi^* = .5\times10^{-7}; \mu = 0.5; C = 10^7; dtime = 0.1$
$\phi = 0.01$
$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 40\times10^5 & \text{for } 2 < t \le 3, \\ 0 & \text{for } t \ge 3 \end{cases}$
Moments start at steady state values for τ=0

Figure 15

YOUNG CELL PAIRS

MEAN NUMBER OF YOUNG CELL PAIRS



Parameters

$old: \upsilon_o^* = 0.05\times10^{-7};\ \eta_o^* = 10^{-7};\ \kappa_o^* = 10^{-7};\ \lambda_o = .08$

$new: \upsilon_n^* = .1\times10^{-7};\ \eta_n^* = .5\times10^{-7};\ \kappa_n^* = 10^{-7};\ \lambda_n = .05$

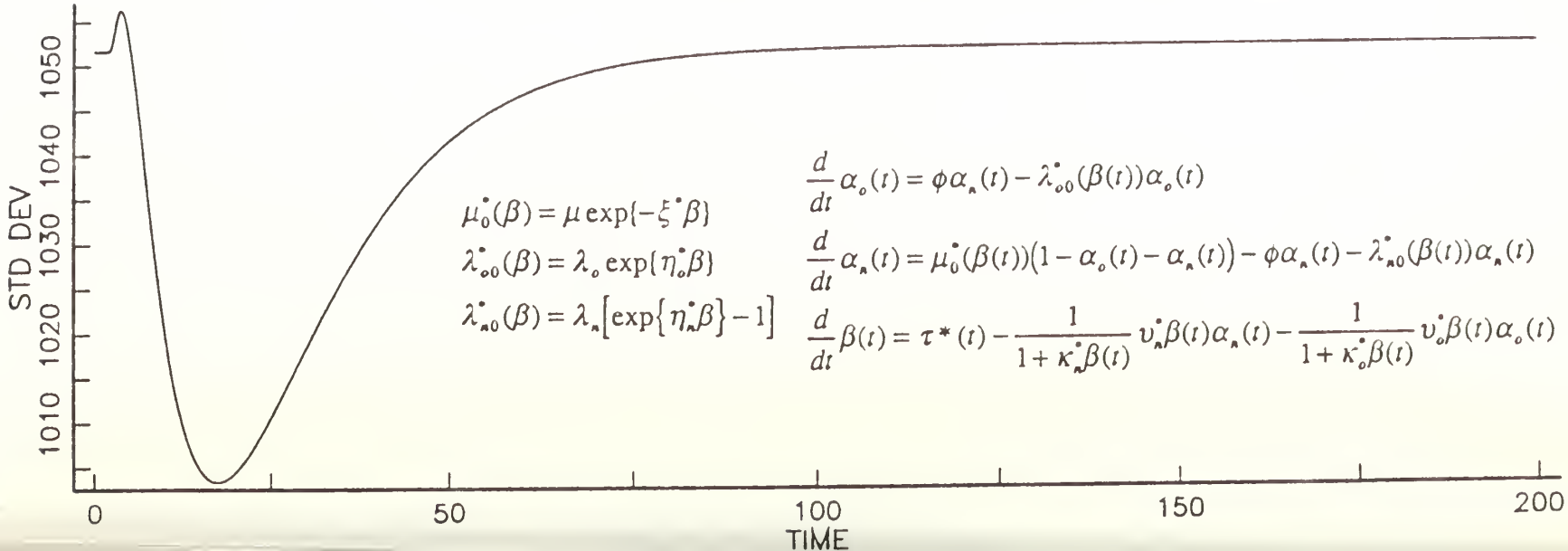
$\xi^* = .5\times10^{-7};\ \mu = 0.5;\ C = 10^7;\ dtime = 0.1$

$\phi = 0.01$

$$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 40\times10^5 & \text{for } 2 < t \le 3, \\ 0 & \text{for } t \ge 3 \end{cases}$$

Moments start at steady state values for τ=0

STD DEV OF NUMBER OF YOUNG CELL PAIRS



$$\mu_0^*(\beta) = \mu\exp\{-\xi^*\beta\}$$

$$\lambda_{oo}^*(\beta) = \lambda_o\exp\{\eta_o^*\beta\}$$

$$\lambda_{no}^*(\beta) = \lambda_n\left[\exp\{\eta_n^*\beta\} - 1\right]$$

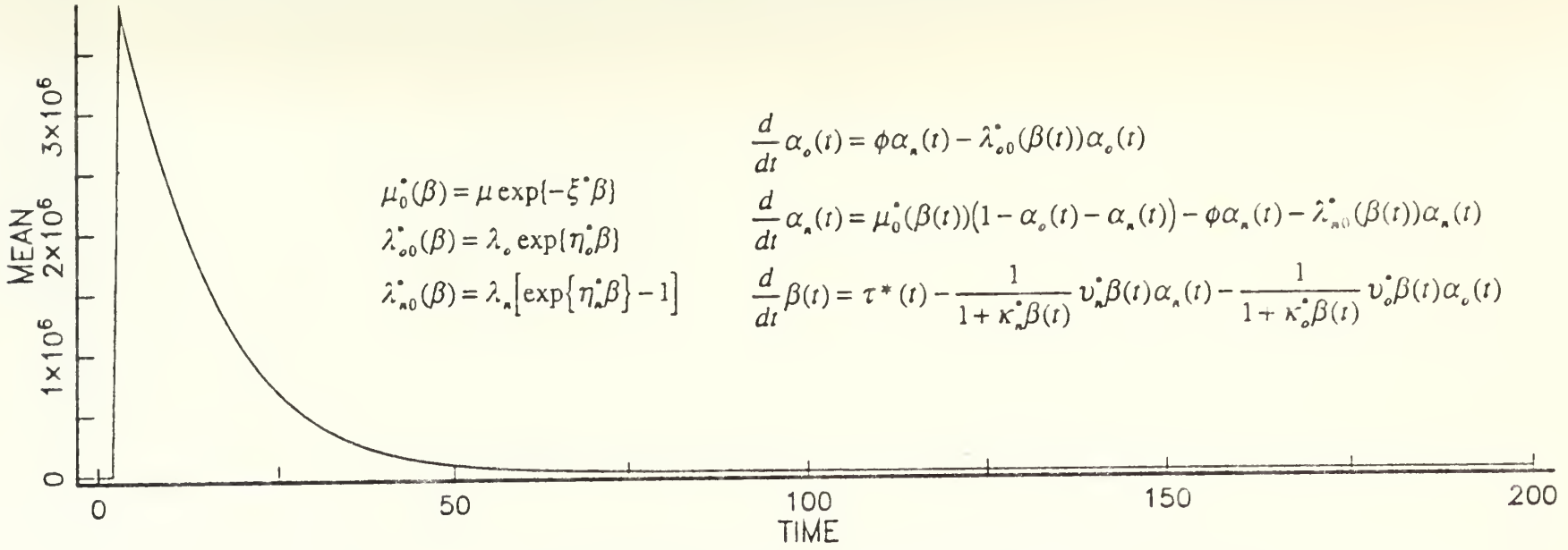
$$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{oo}^*(\beta(t))\alpha_o(t)$$

$$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1-\alpha_o(t)-\alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{no}^*(\beta(t))\alpha_n(t)$$

$$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$$

AMOUNT OF TOXIN

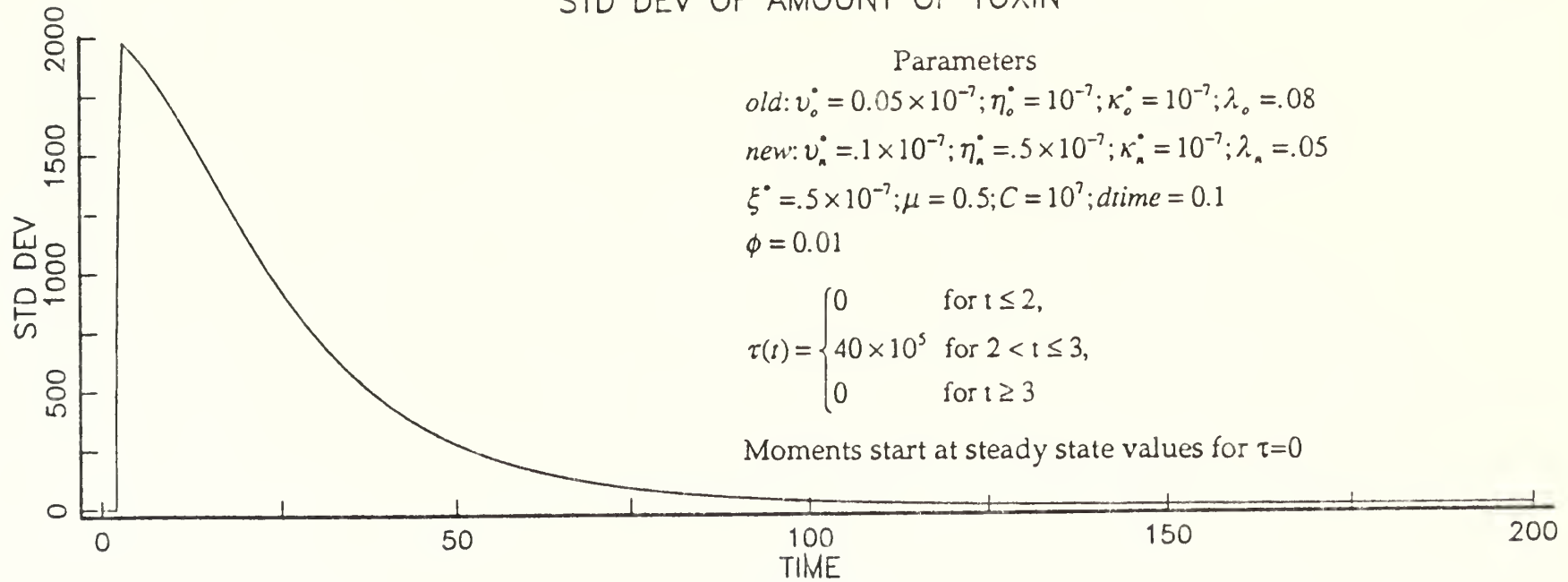
MEAN AMOUNT OF TOXIN



$$\mu_0^*(\beta) = \mu \exp\{-\xi^*\beta\}$$
$$\lambda_{o0}^*(\beta) = \lambda_o \exp\{\eta_o^*\beta\}$$
$$\lambda_{n0}^*(\beta) = \lambda_n\left[\exp\{\eta_n^*\beta\} - 1\right]$$

$$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{o0}^*(\beta(t))\alpha_o(t)$$
$$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1 - \alpha_o(t) - \alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{n0}^*(\beta(t))\alpha_n(t)$$
$$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$$

STD DEV OF AMOUNT OF TOXIN



Parameters

old: $\upsilon_o^* = 0.05\times10^{-7}; \eta_o^* = 10^{-7}; \kappa_o^* = 10^{-7}; \lambda_o = .08$

new: $\upsilon_n^* = .1\times10^{-7}; \eta_n^* = .5\times10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$

$\xi^* = .5\times10^{-7}; \mu = 0.5; C = 10^7; dtime = 0.1$

$\phi = 0.01$

$$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 40\times10^5 & \text{for } 2 < t \le 3, \\ 0 & \text{for } t \ge 3 \end{cases}$$

Moments start at steady state values for τ=0

Figure 17

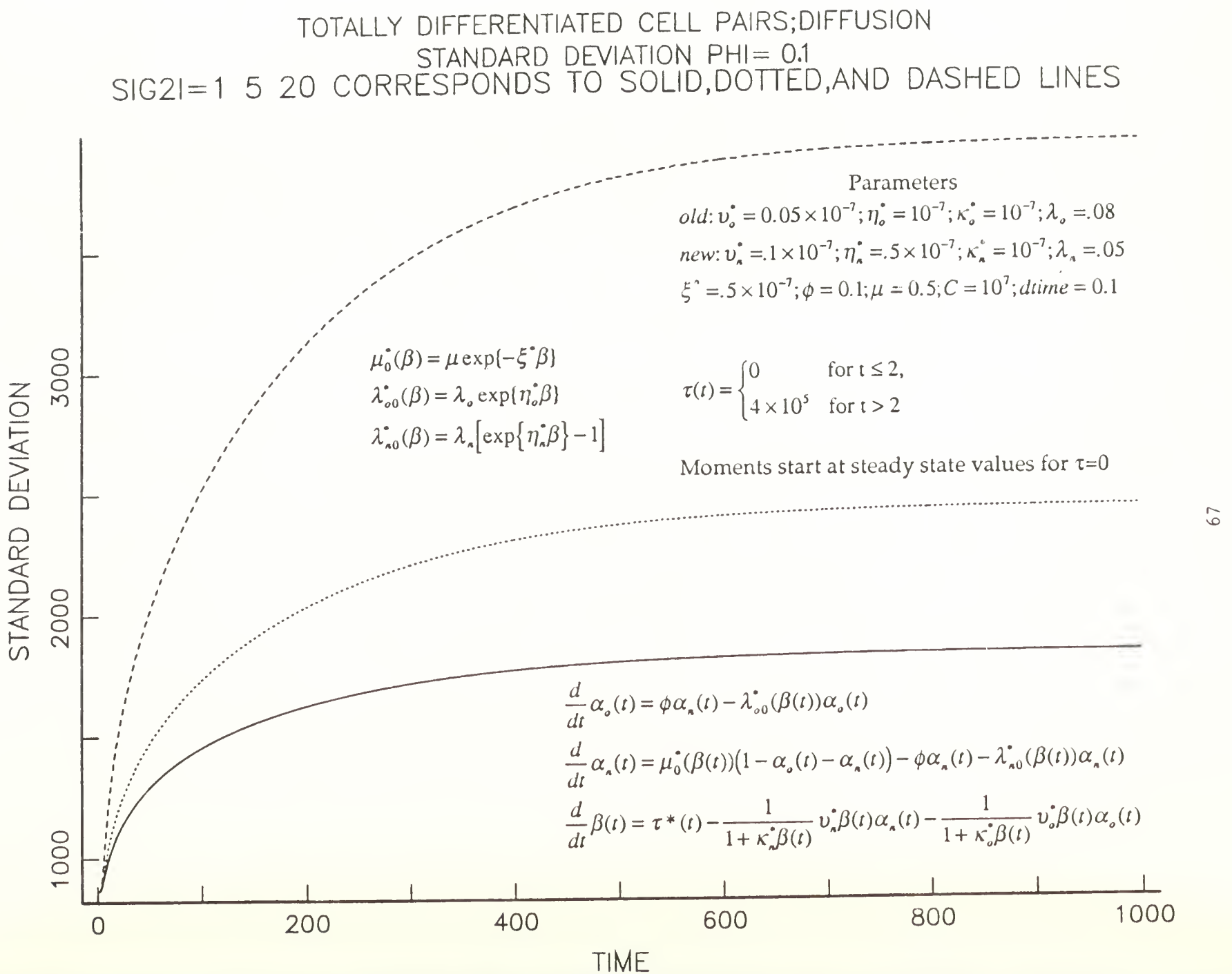
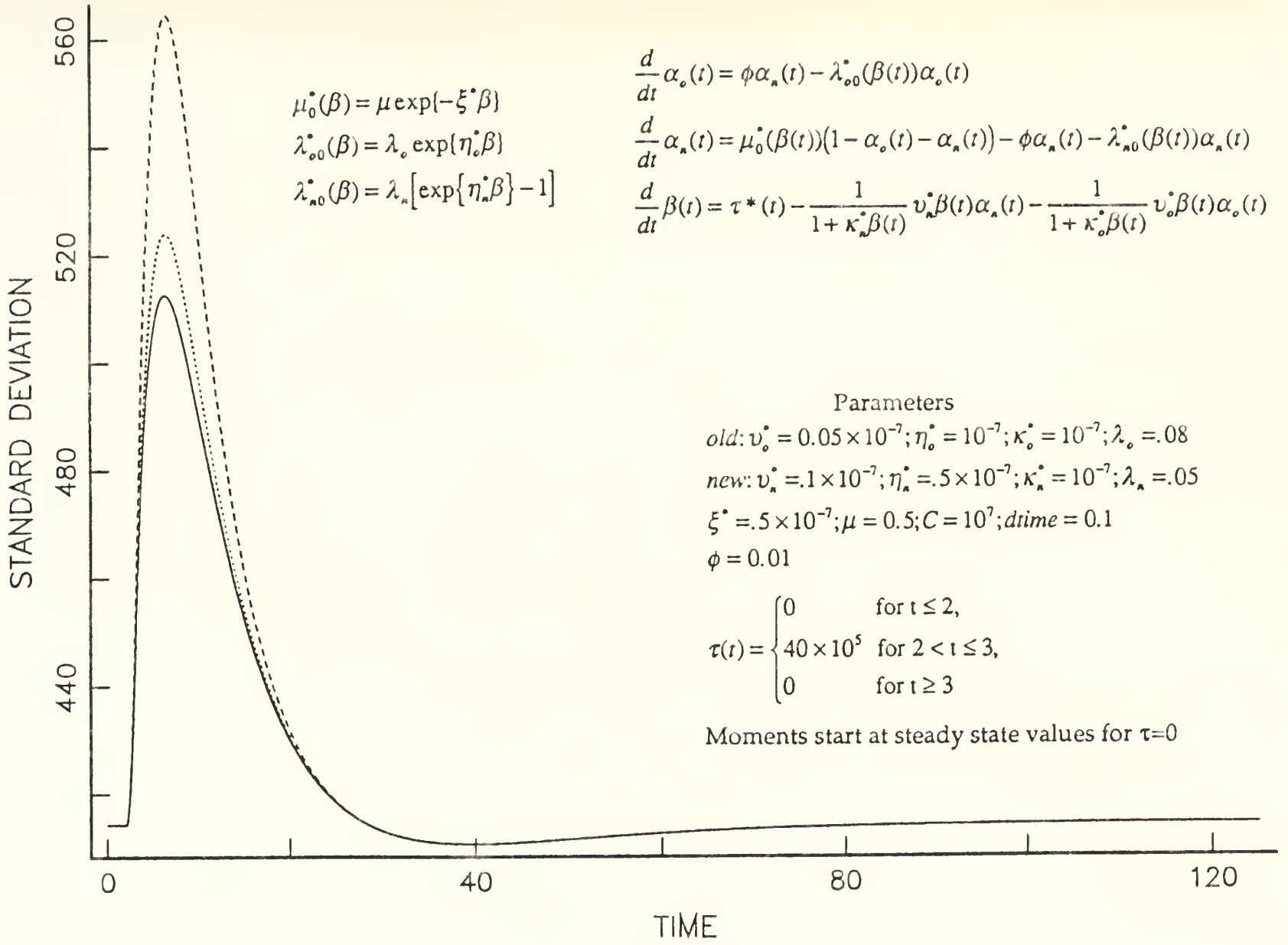

TOTALLY DIFFERENTIATED CELL PAIRS;DIFFUSION
STANDARD DEVIATION PHI= 0.1
SIG2I=1 5 20 CORRESPONDS TO SOLID,DOTTED,AND DASHED LINES
STANDARD DEVIATION
1000
2000
3000
0
200
400
600
800
1000
TIME
Parameters
old: $\upsilon_o^* = 0.05\times10^{-7};\ \eta_o^* = 10^{-7};\ \kappa_o^* = 10^{-7};\ \lambda_o = .08$
new: $\upsilon_n^* = .1\times10^{-7};\ \eta_n^* = .5\times10^{-7};\ \kappa_n^* = 10^{-7};\ \lambda_n = .05$
$\xi^* = .5\times10^{-7};\ \phi = 0.1;\ \mu = 0.5;\ C = 10^7;\ dtime = 0.1$
$\mu_0^*(\beta) = \mu\exp\{-\xi^*\beta\}$
$\lambda_{o0}^*(\beta) = \lambda_o\exp\{\eta_o^*\beta\}$
$\lambda_{n0}^*(\beta) = \lambda_n\left[\exp\{\eta_n^*\beta\} - 1\right]$
$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 4\times10^5 & \text{for } t > 2 \end{cases}$
Moments start at steady state values for τ=0
$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{o0}^*(\beta(t))\alpha_o(t)$
$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))(1-\alpha_o(t)-\alpha_n(t)) - \phi\alpha_n(t) - \lambda_{n0}^*(\beta(t))\alpha_n(t)$
$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$

Figure 1B

TOTALLY DIFFERENTIATED CELL PAIRS;DIFFUSION
STANDARD DEVIATION PHI=.01
SIG2I=1 5 20 CORRESPONDS TO SOLID,DOTTED,AND DASHED LINES



$$\mu_0^*(\beta) = \mu \exp\{-\xi^* \beta\}$$
$$\lambda_{o0}^*(\beta) = \lambda_o \exp\{\eta_o^* \beta\}$$
$$\lambda_{n0}^*(\beta) = \lambda_n \left[\exp\{\eta_n^* \beta\} - 1\right]$$

$$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{o0}^*(\beta(t))\alpha_o(t)$$
$$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1 - \alpha_o(t) - \alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{n0}^*(\beta(t))\alpha_n(t)$$
$$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$$

Parameters

old: $\upsilon_o^* = 0.05\times10^{-7}; \eta_o^* = 10^{-7}; \kappa_o^* = 10^{-7}; \lambda_o = .08$

new: $\upsilon_n^* = .1\times10^{-7}; \eta_n^* = .5\times10^{-7}; \kappa_n^* = 10^{-7}; \lambda_n = .05$

$\xi^* = .5\times10^{-7}; \mu = 0.5; C = 10^7; dtime = 0.1$

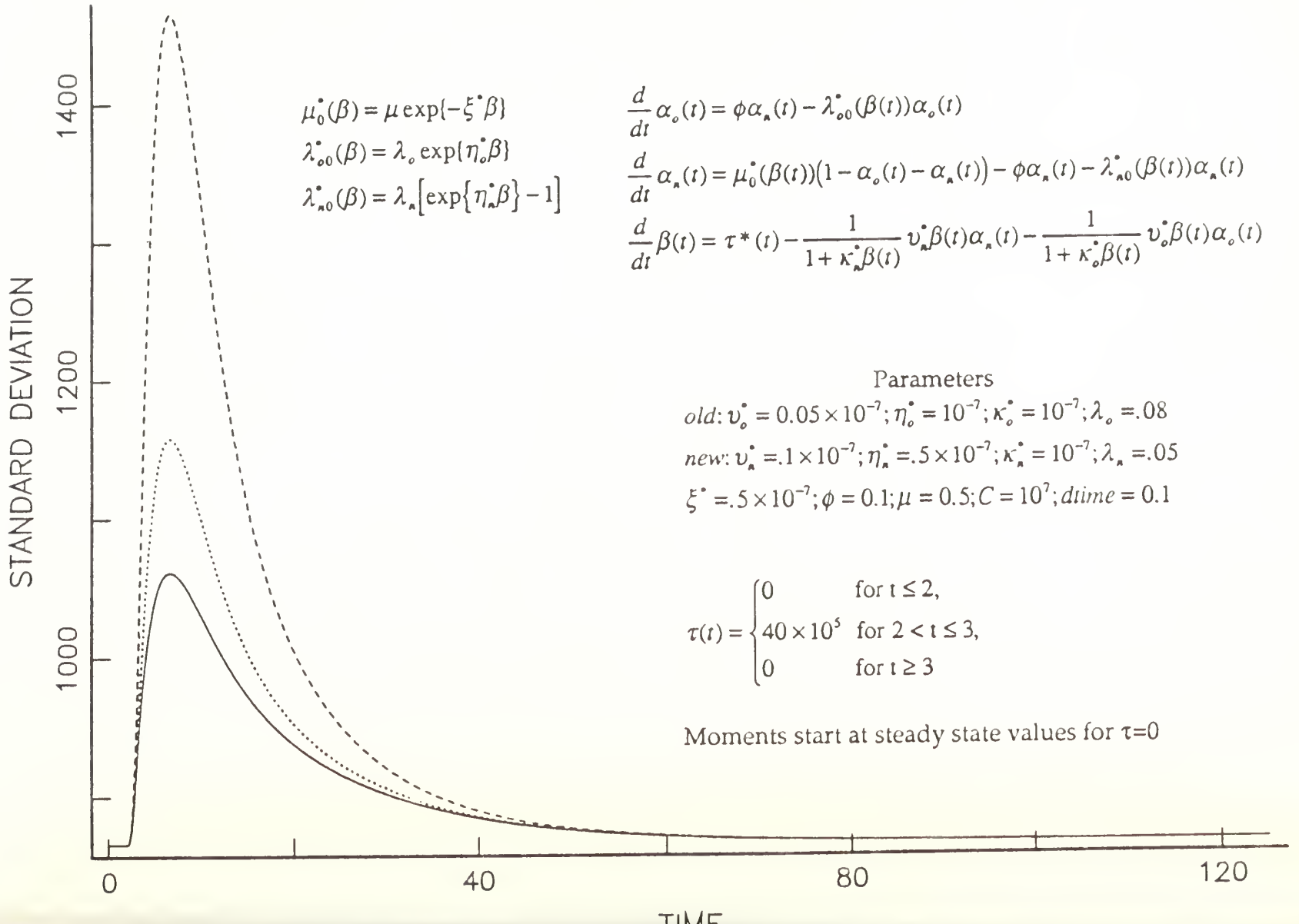
$\phi = 0.01$

$$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 40\times10^5 & \text{for } 2 < t \le 3, \\ 0 & \text{for } t \ge 3 \end{cases}$$

Moments start at steady state values for τ=0

Figure 2B

TOTALLY DIFFERENTIATED CELL PAIRS;DIFFUSION
STANDARD DEVIATION
SIG2I=1 5 20 CORRESPOND TO SOLID,DOTTED,DASHED LINES



$$\mu_0^*(\beta) = \mu \exp\{-\xi^* \beta\}$$
$$\lambda_{oo}^*(\beta) = \lambda_o \exp\{\eta_o^* \beta\}$$
$$\lambda_{no}^*(\beta) = \lambda_n \left[\exp\{\eta_n^* \beta\} - 1\right]$$

$$\frac{d}{dt}\alpha_o(t) = \phi\alpha_n(t) - \lambda_{oo}^*(\beta(t))\alpha_o(t)$$
$$\frac{d}{dt}\alpha_n(t) = \mu_0^*(\beta(t))\left(1 - \alpha_o(t) - \alpha_n(t)\right) - \phi\alpha_n(t) - \lambda_{no}^*(\beta(t))\alpha_n(t)$$
$$\frac{d}{dt}\beta(t) = \tau^*(t) - \frac{1}{1+\kappa_n^*\beta(t)}\upsilon_n^*\beta(t)\alpha_n(t) - \frac{1}{1+\kappa_o^*\beta(t)}\upsilon_o^*\beta(t)\alpha_o(t)$$

Parameters

old: $\upsilon_o^* = 0.05\times10^{-7}$; $\eta_o^* = 10^{-7}$; $\kappa_o^* = 10^{-7}$; $\lambda_o = .08$

new: $\upsilon_n^* = .1\times10^{-7}$; $\eta_n^* = .5\times10^{-7}$; $\kappa_n^* = 10^{-7}$; $\lambda_n = .05$

$\xi^* = .5\times10^{-7}$; $\phi = 0.1$; $\mu = 0.5$; $C = 10^7$; $dtime = 0.1$

$$\tau(t) = \begin{cases} 0 & \text{for } t \le 2, \\ 40\times10^5 & \text{for } 2 < t \le 3, \\ 0 & \text{for } t \ge 3 \end{cases}$$

Moments start at steady state values for τ=0

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